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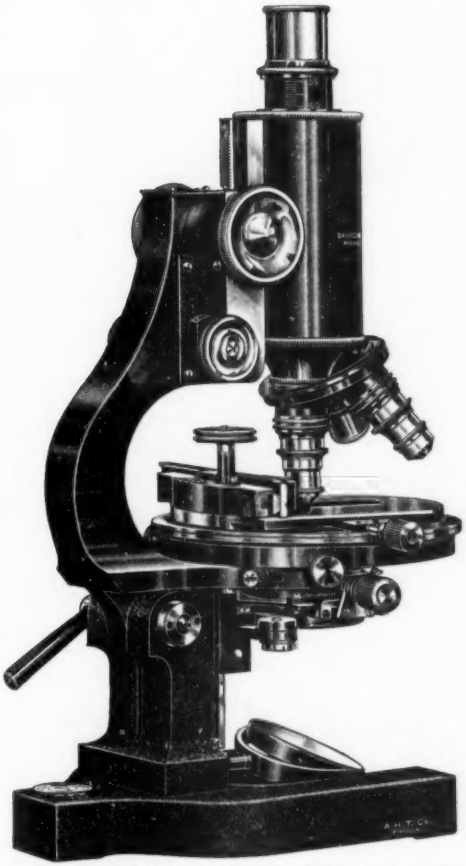

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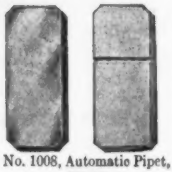

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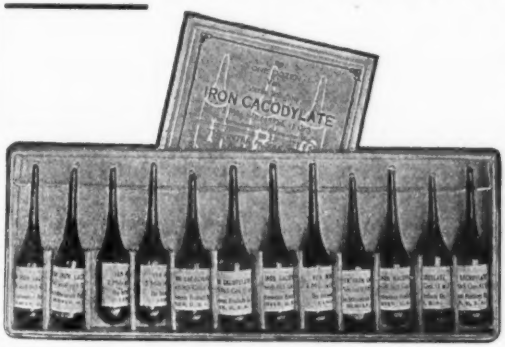

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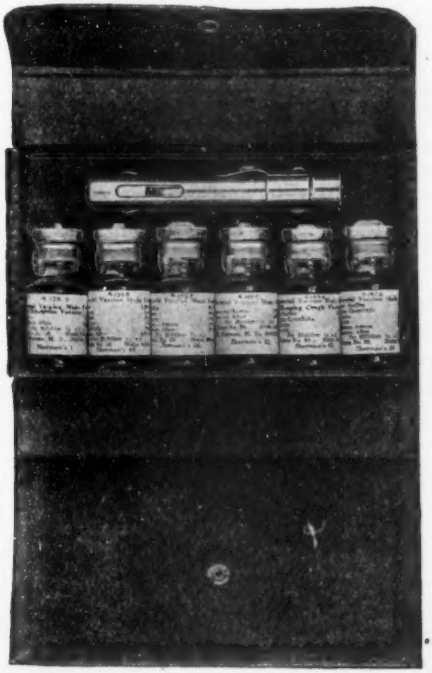

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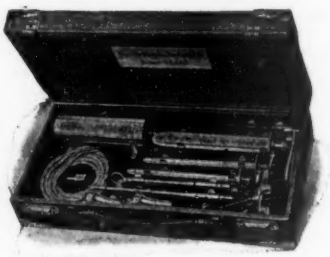

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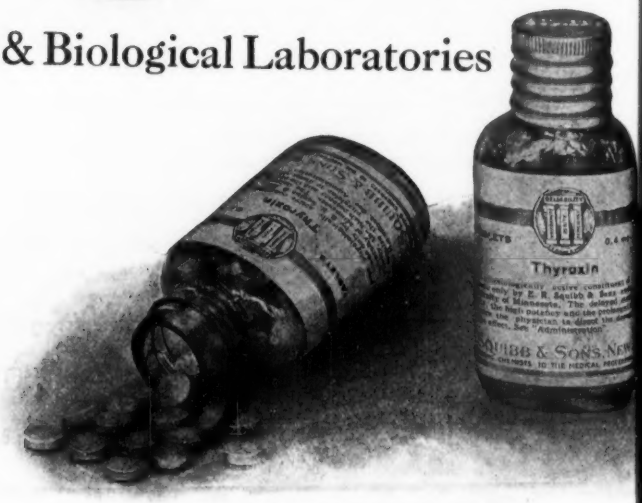

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AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1920

ORIGINAL ARTICLES.

EXPERIMENTAL STUDIES IN DIABETES: SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION TO BODY MASS AND METABOLISM.

I. ALTERATIONS OF CARBOHYDRATE ASSIMILATION BY REMOVAL OF PORTIONS OF THE PANCREAS.

By Frederick M. Allen, M.D.,

NEW YORK.

(From the Hospital of the Rockefeller Institute for Medical Research, New York.)

The preceding series of papers[1] gave a general outline of the checking of diabetes by fasting and restriction of total diet on the current theory of sparing the weakened pancreatic function. This speculative clinical hypothesis thus received positive physiologic and anatomic demonstration, so that the possibility of damaging the islands of Langerhans by functional overstrain and saving them by limiting the dietary burden stands as an established fact. At the same time the vagueness of this language is unfortunate and more information is desirable concerning the nature of the island function and the processes involved in overtaxing and resting it. This need is both theoretical, for understanding the endocrine role of the pancreas, and practical, for the most accurate and effective application of treatment. The same observations also afford the opportunity for such a study by furnishing plain physiologic and anatomic criteria by which the effect of various influences upon the islands can be judged.

[1] Allen, F. M.: Jour. Exper. Med., 1920, vol. xxxi.

As shown elsewhere, an explanation of the effect of fasting is not found in any gross or microscopic alterations in the pancreas; in particular there is no evidence of an increase of islands by fasting. The changes in question must be sought elsewhere in the body. The known effects of fasting and low diet are a reduction of body weight and metabolism. Each of these may be subdivided.

(*a*) The reduction of weight may pertain either to storage materials or to active protoplasm. It may seem natural that a reduction of stored foods should increase the capacity of the body to receive food. As a matter of fact no such rule has been demonstrable for the normal organism, particularly with reference to the most easily excreted food, carbohydrate. The utmost glycogen storage does not lower the sugar tolerance. On the contrary a dose of glucose improves the assimilation of a closely succeeding dose.[2] Though respiration studies indicate that fasting creates a tendency to storage of carbohydrate as opposed to combustion,[3] the tendency to hyperglycemia and glycosuria is notoriously increased by either fasting or carbohydrate-free diet.[4] Evidently some state of preparedness of the organism is here more determining than the mere fulness or emptiness of the depots.

(*b*) A reduction of active protoplasm may receive two opposite interpretations. On the one hand it may be supposed that reduction of the living matter which carries on metabolism will involve a reduced capacity for metabolism. On the other hand a quantitative relation may be conceived between the mass of pancreas and the mass of tissue which it can supply. As the pancreas of a mouse could not possibly suffice for the body of an elephant, the same principle may hold for less extreme differences; and when the pancreatic hormone is deficient the relatively greater supply resulting from a diminution of protoplasm may facilitate metabolism.

(*c*) Metabolism likewise may be variously regarded in this connection. Distinctions may be drawn between the metabolism of matter and of energy, and in the broadest sense between the exogenous or external activities of the cells and their endogenous or structural metabolism. The relation of the pancreatic function to the three chief food substances, carbohydrate, protein and fat, is also involved. In addition the influence of the other endocrine organs which affect metabolism requires consideration.

All the above relations are capable of experimental modification in various ways. Having the above criteria of pancreatic function, it is a simple matter to perform a series of experiments to furnish

[2] Hamman, L., and Hirschman, I. I.: Bull. Johns Hopkins Hosp., 1919, xxx, 306.

[3] Johansson, J. E., Billström, J., and Heijl, C.: Skand. Arch. Physiol., 1904, xvi, 263–272. Johansson: Ibid., 1909, xxi, 1–34. Falta, W.: Med. Klin., 1914, x, 9.

[4] Hofmeister, F.: Arch. exp. Path. u. Pharm., 1889–90, xxvi, 355. Allen, F. M.: Glycosuria and Diabetes, 1913, Chapter XIII; Jour. Exp. Med., 1920, xxxi, 557.

some information concerning this function. One group of such experiments was planned to investigate the quantitative relations of this function with the body mass and metabolism, the latter two being viewed theoretically as separate though never strictly separable in practice. Intimately connected with this problem are questions of the nature of the function: whether the quantitative relation is with food, so that a certain quantity of the internal secretion is necessary for the utilization of a certain quantity of food, or with the cells, so that they require a certain minimum quantity of the secretion, and if possessing it can metabolize indefinite quantities of food; whether the function pertains primarily to carbohydrate alone or also to protein and fat; and other questions of this character concerning the mechanism of the internal pancreatic secretion and its place in metabolism. As far as possible the experiments dealing with quantitative relations between the pancreas and the occurrence of diabetes or certain characteristic diabetic phenomena have been grouped in the present series, of which papers 1 to 4 are published in this JOURNAL and papers 5 to 12 in the *American Journal of Physiology*. Other series pertaining to the nature of the endocrine pancreatic function are presented in other journals.

The most direct means of altering the relation between pancreas mass and body mass is by surgical resections. The first experiments of the series deal with the removal of various portions of the pancreas and observations of the tolerance for Merck's anhydrous glucose by stomach and by subcutaneous injection in 30 per cent. solution. The usual precautions and standardized conditions were employed.* Unless otherwise specified the diet was bread and soup *ad libitum* and the tests were performed after twenty-four hours' fasting. The urinary sugar was determined by titration with Benedict's solution and the blood sugar by the method of Lewis and Benedict.

REMARKS ON DOG B2–00.

1. The above dog received various doses of Merck glucose by stomach tube and subcutaneously after removal of successive portions of the pancreas, the standard of tolerance being the smallest quantity with which distinct glycosuria could be produced. The first removal of 7.1 gm. from the splenic end, representing between a fourth and a third of the pancreas, resulted in a perceptible lowering of tolerance by this test, so that glycosuria resulted from the injection of as little as 2.5 gm. per kgm. when it had formerly been absent with as much as 9 gm. per kgm. Further reductions of the tolerance followed the removal of further portions of the pancreas.

* All operations were performed under ether anesthesia.

TABLE I.—DOG. B2-00. WEIGHT 14 KGM.

Date, 1913.	Glucose dosage, gm. per kgm.	Hours following injection.	Glycosuria, gm.	Plasma sugar, per cent.	Remarks.
Nov. 1	8.0	24	Faint	..	Subcutaneous injection; normal dog.
8	6.0	24	Slight	..	Subcutaneous injection.
13	2.0	24	0	..	Subcutaneous injection.
17	7.0	24	0	..	Stomach tube.
20	7.0	24	0	..	Subcutaneous injection.
29	9.0	24	0	..	Subcutaneous injection.
Dec. 8	Removed pancreatic tissue weighing 7.1 gm., consisting of most of the splenic end.				
20	6.0	6	0.4	..	Subcutaneous injection.
		24	Faint		
30	4.5	24	0.3	..	Subcutaneous injection.
1914.					
Jan. 2	3.0	24	0.2	..	Subcutaneous injection.
5	2.5	24	0.2	..	Subcutaneous injection.
9	1.8	24	0	..	Subcutaneous injection.
13	4.0	1½	Faint	..	Stomach tube.
		3	Faint	..	
		24	0		
Jan. 19	Removed processus uncinatus weighing 4 gm.				
Feb. 5	2.0	5½	Faint	..	Subcutaneous injection.
		24	0		
11	1½	4	Slight	..	Subcutaneous injection.
		24	Faint		
Mar. 26	1½	6	Faint	..	Subcutaneous injection.
		24	0		
April 3	2.1	24	Faint	..	Subcutaneous injection.
20	2.4	6	Faint	..	Subcutaneous injection; this injection given two hours after feeding.
		24	0		
27	2.4	6	Faint	..	Subcutaneous injection.
		24	0		
May 19	2.7	4	Faint	..	Subcutaneous injection.
		24	0		
27	3.0	7½	Faint	..	Subcutaneous injection.
		24	0		
June 2	4.0	24	Faint	..	Subcutaneous injection.
8	5.0	24	Faint	..	Subcutaneous injection.
26	6.0	24	Negative	..	Subcutaneous injection.
July 2	6.0	1½	0	..	Stomach tube.
		3½	0		
		24	0		
8	7.0	2	Faint	..	Subcutaneous injection.
		24	0.34		
30	7.0	3	0	..	Stomach tube.
		24	0		
Nov. 9	7.0	2½	Slight	..	Subcutaneous injection.
		24	Slight		
Dec. 10	Removed stump of the processus lienalis and adjoining part of corpus, weighing 6.3 gm.				
1915.					
Mar. 16	6.0	24	0	..	Subcutaneous injection.
June 2	3.0	3	Slight	..	Subcutaneous injection.
		8	0.69		
		12	0.82		
		24	Faint		
11	1.5	4	0	..	Subcutaneous injection.
		8½	0		
		10	0		
		24	0		
18	3.0	1	0	..	Stomach tube.
		7	0		
		9	0		
		24	0		
30	4.0	22½	0	..	Subcutaneous injection.
1916.					
Sept. 6	Removed 0.8 gm. pancreatic tissue.				
Nov. 15	4.0	2	0.26	..	Stomach tube.
		3½	0		
20		Before feeding	0	0.102	Fed 200 gm. bread.
		2	0	0.125	100 gm. lung.
		4	0.36	0.154	75 gm. glucose.
		6	0	0.149	
21		Before feeding	0	0.106	Fed 200 gm. bread.
		2	0	0.123	100 gm. lung.
		4	Faint	0.156	150 gm. glucose.
		6	Faint	0.128	
23		Before feeding	0	0.092	Fed 200 gm. bread.
		2	0	0.095	100 gm. lung.
		4	0	0.139	150 gm. glucose.
		6	0	0.130	

TABLE I.—DOG. B2–09. WEIGHT 14 KGM. (Continued).

Date, 1916.	Glucose dosage, gm. per kgm.	Hours following injection.	Glycosuria, gm.	Plasma sugar, per cent.	Remarks.
Dec. 16	Removed 0.1 gm. of pancreatic tissue.			Dog pregnant.	
30		Before feeding	0	0.085	Fed 200 gm. bread.
		2	3.45	0.345	100 gm. lung.
		4	6.46	0.455	150 gm. glucose.
		6	5.89	0.500	
1917.					
Jan. 7	..	Before feeding	0	0.125	Fed 200 gm. bread.
		2	7.13	0.400	100 gm. lung.
		4	6.68	0.400	150 gm. glucose.
		6	8.0	0.333	
Feb. 23		Before feeding	0	0.116	Fed 200 gm. bread.
		2	0.63	0.238	100 gm. lung.
		4	0.57	0.244	150 gm. glucose.
		6	0.69	0.232	

2. There are irregularities in individual tests. For example, the slight reaction with 6 gm. per kgm. on November 8, 1913, is an instance of accidental variation, and it is probable that the dog was slightly nervous during the first two tests. On January 5, 1914, there was glycosuria with 2.5 gm. per kgm. and in February and March with 1.5 gm. per kgm., while on June 26 and the ensuing March 16, after removal of more pancreatic tissue, as much as 6 gm. per kgm. was tolerated. These discrepancies with subcutaneous injection were paralleled by those found with the stomach tube administration. Possibly a real recovery of pancreatic function during the long period of time may be the reason. In general the decline of tolerance is evident as mentioned.

3. As the verge of diabetes was approached small fragments of pancreatic tissue acquired great importance. Prolonged carbohydrate-rich diet (June 30, 1915, to September 6, 1916) did not bring on diabetes. On the latter date the tolerance was perceptibly lowered by the removal of 0.8 gm. pancreatic tissue, which could never have been missed if removed from a normal animal. Diabetes was caused by the removal of only 0.1 gm. of tissue on December 16. Some influence may be attributed to the attendant inflammatory injury, but the inflammation produced by the careful removal of such a small bit of tissue is very slight.

4. Blood-sugar analyses were impossible at first but were introduced as soon as facilities permitted. They serve for little more than rough indication of the height and duration of hyperglycemia and to exclude any extraordinary slowness of absorption or variations of renal permeability. With the increasing delicacy of tests necessary at this stage, factors of this sort assumed such importance that recourse was had to intravenous tests in other animals, as described elsewhere.[5] The methods employed for the present animals were discontinued and for other reasons some feeding experiments were performed, which are appended for their interest in the present connection. The complication introduced by pregnancy is discussed in a subsequent paper (No. 9 of this series).

[5] Allen, F. M., and Wishart, Mary B.: Jour. Biol. Chem., 1920, xlii, 415.

5. These feeding experiments, from November 15 to November 23, 1916, show that although the apparent tolerance theretofore had been lowered so that glycosuria resulted from 4 gm. or less of glucose per kgm., the actual tolerance was so high that only moderate hyperglycemia and trivial glycosuria resulted from as much as 100 gm. beef lung, 200 gm. bread and 150 gm. glucose.* As a matter of fact the attempt to produce continuous glycosuria or lowering of assimilation by the highest and most prolonged possible feeding of bread and glucose failed and the tolerance actually rose as indicated by the results in blood and urine on November 23 in comparison with the preceding days. The removal of the tiny fragment of pancreatic tissue on December 16 produced a decisive change, as shown in two ways: (1) The difference in hyperglycemia and glycosuria on the identical diet is striking and on a different plane from anything following the former operations; (2) the tendency to loss of tolerance was progressive. Slight glycosuria resulted from plain bread and soup diet, so that the diet had to be changed to beef lung. With this sparing of the function and termination of the pregnancy, improvement of assimilation was possible. Such progressive improvement was shown in the tests from December 30, 1916, to February 23, 1917, in Table I, and still more in the later ones reported in paper 3 of Series I. As there recorded the identical diet on August 9 and October 5, 1917, gave results in blood and urine practically the same as those in November, 1916. The great actual difference in condition is shown by the later history of the dog as given in the paper mentioned, for the mere prolonged continuance of a high-calory carbohydrate-free diet gradually broke down the tolerance. An agreement of physiologic and anatomic evidence thus indicates the excessive labor of an inadequate pancreas remnant in the attempt to prove equal to its task and its gradual breakdown under the strain.

This observation harmonizes with that made with the glucose tests under (2) above, where there was an apparent rise of tolerance, though the animal after removal of more pancreatic tissue must have been closer to diabetes. The conclusion must be that though some approximate information is derivable from such assimilation tests, neither the administration of glucose by stomach or subcutaneously nor the feeding of a mixed meal is necessarily decisive concerning the precise state of an animal as respects diabetes.

Remarks on Dog B2–01.

Essentially the same points are noted as in Dog B2–00. The largest subcutaneous dose which the normal animal assimilated

* The distinction between these traces of glycosuria and the genuine limits of assimilation is illustrated further by the test of April 20, 1914, when the assimilation of 6 gm. glucose per kgm. subcutaneously was not perceptibly lowered by giving it two hours after the dog had eaten her fill of bread and soup.

without glycosuria was 7 gm. per kilo. After removal of only the splenic process, glycosuria resulted from 3 gm., but not from 2.5 gm. per kilo. After removal of the uncinate process there was glycosuria with 1.5 gm. per kilo.

TABLE II.—DOG B2-01. WEIGHT 14 KGM.

Date.	Glucose dosage, gm. per kgm.	Hours following injection	Plasma sugar, per cent.	Glycosuria, gm.	Remarks.
1913.					
Nov. 1	8.0	24	..	Slight	Subcutaneous injection; normal dog.
11	4.0	24	..	0	Subcutaneous injection; normal dog.
16	8.0	2	..	1.30	Stomach tube.
20	7.0	5	..	0	Subcutaneous injection.
		24	..	0	
29	9.0	6	..	Slight	Subcutaneous injection.
		24	..	0	
Dec. 6	8.0	5½	..	0.60	Subcutaneous injection.
		24	..	Slight	
12	Removed processus lienalis, weighing 8 gm; estimated as little less than one-third pancreas.				
21	4.5	6	..	0	Subcutaneous injection.
		24	..	Slight	
30	4.5	24	..	0.40	Subcutaneous injection.
1914.					
Jan. 2	3.0	24	..	0.80	Subcutaneous injection.
5	2.5	24	..	0	Subcutaneous injection.
13	4.0	1	..	Faint	Subcutaneous injection.
		2	..	0	
		24	..	0	
20	Removed processus uncinatus of pancreas, weighing 5.9 gm.				
Feb. 5	2.0	5	..	0.12	Subcutaneous injection.
		24	..	0	
11	1.5	4	..	Slight	Subcutaneous injection.
		24	..	Faint	
Mar. 26	1.5	6	..	Faint	Subcutaneous injection.
		24	..	0	
April 3	2.1	24	..	Faint	Subcutaneous injection.
20	2.4	6	..	Slight	Subcutaneous injection; fed bread and soup four hours before test.
		24	..	0	
27	2.4	6	..	0	Subcutaneous injection.
		24	..	0	
May 15	Removed splenic end of body, weighing 7 gm.				
June 1	2.0	24	..	Faint	Subcutaneous injection.
8	4.0	24	..	Faint	Subcutaneous injection.
July 9	6.0	2	..	0.72 (2.40%)	Stomach tube.
		24	..	0	
13	4.0	2	..	Faint	Stomach tube.
		24	..	0	
17	7.0	2	..	0.27 (2.70%)	Subcutaneous injection.
		24	..	Slight	
Nov. 9	7.0	2	..	1.20 (5.00%)	Subcutaneous injection.
		24	..	1.20 (2.00%)	
24	Removed pancreatic tissue weighing 1.25 gm.				
1915.					
April 30	4.0	Before feeding	0.107	0	Stomach tube.
		½	0.244	0.03 (0.25%)	
		1	0.250	0.07 (2.27%)	
		2½	0.266	0.45 (5.50%)	
		4½	..	0.92 (7.10%)	
		6	0.184	1.00 (8.30%)	
		8	0.324	0.23 (2.40%)	
		10	0.230	0.11 (0.70%)	
		12	..	Faint	
		13	0.186	Faint	
		15	0.163	Faint	
		24	0.146	0	
Sept. 29	4.0	Before feeding	0.106	0	
		1½	0.256	Slight	Stomach tube.
		3½	0.147	Faint	
		7	0.103	0	
1916.					
April 26	Removed pancreatic tissue weighing 0.85 gm.				
Aug. 31	Removed pancreatic tissue weighing 0.80 gm.				
Nov. 15		2	..	1.10 (6.30%)	Stomach tube.
	4.0	5½	..	1.70 (4.60%)	
		24	..	0	

The retention of actual assimilative power was shown on April 20, 1914, when the tolerance for 2.4 gm. glucose per kilo was scarcely altered (as compared with April 27) by a full meal of bread and soup four hours before the subcutaneous injection. After removal of 7 gm. additional pancreatic tissue there was a tendency to a rise of the apparent tolerance, as indicated by the trivial glycosuria from 4 gm. glucose per kilo on June 8 and July 13; but the dog was approaching the border of diabetes, as shown by the marked effect on removing 1.25 gm. tissue on November 24. Nevertheless, prolonged high starch and glucose diets were unable to produce any

TABLE III.—DOG B2-02. WEIGHT 10.5 KGM.

Date.	Glucose dosage, gm. per kgm.	Hours following injection.	Glycosuria, gm.	Remarks.
1913.				
Nov. 1	8.0	24	Slight	Subcutaneous injection; normal dog.
11	4.0	24	Slight	Subcutaneous injection.
15	8.0	1	Faint	Stomach tube.
		24	0	
20	7.0	5	0	Subcutaneous injectic .
		24	0	
22	10.0	4	0	Stomach tube.
		24	0	
29	9.0	6½	0.4	Subcutaneous injection.
		24	0	
Dec. 6	8.0	5	0.2	Subcutaneous injection.
		24	Slight	
9	Removed processus uncinatus of the pancreas, weighing 6.8 gm.			
22	5.0	6	1.4	Subcutaneous injection.
		24	Slight	
30	3.5	24	Negative	Subcutaneous injection.
1914.				
Jan. 2	4.0	24	Slight	Subcutaneous injection.
13	4.0	1½	Faint	Stomach tube.
		3	0	
		24	0	
20	4.0	5½	Slight	Subcutaneous injection.
		24	0	
23	Removed processus lienalis of the pancreas, weighing 9.7 gm.			
Feb. 5	2.0	5	0.1	Subcutaneous injection.
		24	0	
11	1.5	3½	Slight	Subcutaneous injection.
		24	0	
Mar. 26	1.5	5½	0	Subcutaneous injection.
April 3	2.1	24	Doubtful	Subcutaneous injection.
20	2.4	5½	0	Subcutaneous injection; fed bread and soup three hours before injection.
		24	0	
27	3.0	6½	Faint	Subcutaneous injection.
		24	0	
May 19	3.2	4	Faint	Subcutaneous injection.
		24	Faint	
27	4.0	7	Faint	Subcutaneous injection.
		24	0	
June 2	4.0	24	Faint	Subcutaneous injection.
8	5.0	24	Faint	Subcutaneous injection.
26	6.0	24	0	Subcutaneous injection.
July 2	6.0	2½	0.6	Stomach tube.
		4	0	
		24	0	
7	4.0	3	0.9	Stomach tube.
		24	0	
13	3.0	2	0	Stomach tube.
		24	0	
17	7.0	1½	1.8	Subcutaneous injection.
		24	Faint	
Nov. 9	6.0	2	0.5	Subcutaneous injection.
		24	Slight	
Dec. 10	Removed pancreatic tissue weighing 4.75 gm.			
1915.				
June 2	3.0	24	Faint	Subcutaneous injection.
11	2.0	24	0	Subcutaneous injection.
18	3.0	24	0	Stomach tube.
30	4.0	20	0.8	Subcutaneous injection.

continued glycosuria or lowering of tolerance even with removal of 0.85 gm. additional tissue on April 26, 1916, so that diabetes actually resulted only with the removal of 0.8 gm. tissue on August 31, 1916. This operation caused no immediate striking change in the condition. A lowering of tolerance was indicated by the greater glycosuria from 4 gm. glucose per kilo on November 15 than in the last preceding test by stomach tube. But large carbohydrate meals were still almost completely assimilated and some power of regaining tolerance remained, as indicated by the lower plasma sugars on February 23, 1917, as compared with November 21, 1916. (See record in following paper.) Nevertheless, the downward tendency continued into severe diabetes, as described in the later history.

Remarks on Dog B2-02.

The observations resemble those in the two preceding dogs. The dog tolerated 7 gm. glucose per kilo subcutaneously and as much as 10 gm. per kilo by stomach tube. After the first operation the apparent tolerance subcutaneously lay between 3.5 and 4 gm. per kilo. Thus the removal of the uncinate process was as effective as the removal of the splenic process in the preceding dogs, and it may be remarked that other tests in other dogs have shown no appreciable differences in endocrine potency between different portions of the pancreas. After removal of the splenic process on January 23, 1914, the tolerance fell further so as to lie between 2 and 3 gm. per kilo, but fluctuated somewhat, and as usually the glycosuria, even with much higher dosages, was trivial. Very mild diabetes was produced by the third operation on December 10, 1914. Special mention may be made of two points in this connection: (1) No tests were performed until the following June, when the usual effort at recuperation was evidently in progress, for the apparent tolerance had risen to about 3 gm. per kgm.; (2) the operation to produce diabetes took place much earlier in this dog than in the two preceding and the diabetes occurred with fully as large a pancreas remnant. This animal therefore serves as a control to the other two, to show that the much longer carbohydrate feeding to which they were subjected was not a factor in the production of their diabetes.

The subsequent history of this dog was given in paper 2 of Series I. The evidence of the existence of diabetes was that glycosuria could be readily maintained at any time by the addition of glucose to the diet. The dog would never take glucose long without vomiting, and would eat only moderate quantities of bread, so that she remained free from glycosuria until death from rabies on September 19, 1916. The islands of Langerhans then showed slight vacuolation, so that there would evidently have been an ultimate outbreak of frank diabetes on the diet taken except for the untimely death.

TABLE IV.—DOG B2-43.

Date.	Weight, kgm.	Dosage, gm. per kgm.	Administration.	Glycosuria, gm.	Remarks.
1914.					
Feb. 4	9.2	5.0	Subcutaneousinjection	Faint	Normal dog.
Mar. 26	11.1	5.0	Subcutaneousinjection	Faint	
April 3	10.2	6.0	Subcutaneousinjection	0	
20	11.6	7.0	Subcutaneousinjection	0	
27	10.3	7.0	Subcutaneous injection	0	
May 20	Processus uncinatus stripped of peritoneal covering, vessels ligated.				
June 2	11.0	7.0	Subcutaneous injection	0	
16	Processus uncinatus removed.				
26	9.9	7.0	Subcutaneousinjection	Slight	
July 9	Processus lienalis removed.				
30	10.3	1.0	Stomach tube	0	
Nov. 9	..	4.0	Subcutaneousinjection	Faint	

Remarks on Dog B2-43.

The dog was received in a state of fair nutrition and the original weight of 9.2 kgm. was used as the basis of reckoning dosage throughout. Thus the identical quantity of 46 gm. glucose was injected subcutaneously on February 4 at this weight, and on March 26 after the animal had been fattened to 11.1 kgm. The same trace of glycosuria occurred each time, perhaps from nervousness, for after becoming accustomed to the procedure the dog tolerated 64.4 gm. (7 gm. per kilo) without glycosuria, as she normally should do. The point here is that the changes of weight, which would be sufficient to affect the tolerance of a diabetic dog to a marked degree, had no such influence upon the assimilation of the normal animal.

On May 20 the uncinate process of the pancreas was stripped of peritoneum and the vessels and nerves entering its tip divided—in other words the operation of removal was performed except the actual removal, in order to test whether the lowering of apparent tolerance is due to actual removal of tissue or partly to trauma or nervous or circulatory disturbances. After this, 7 gm. of glucose per kilo was still tolerated without glycosuria; but after actual removal of the uncinate process, on June 16, the same dose caused slight glycosuria. Removal of the splenic process on July 9 lowered the tolerance further, so that on November 9 faint glycosuria followed the injection of 4 gm. per kilo.

Remarks on Dog B2-60.

This Great Dane was fat when received and 45 kilos was assumed as the normal weight on which to reckon dosage throughout. According to paper I of Series I such a large dog would naturally have a small pancreas in proportion to the body weight, and by adding the weights of the portions of pancreas at operations and at autopsy, this particular animal was found to have 1.4 gm. of pancreas per kilo on 45 kilos weight. The tolerance is seen, nevertheless, to be fully as high as that of the normal dogs preceding.

TABLE V.—DOG B2–60.

Date.	Weight, kgm.	Dosage, gm. per kgm.	Administration.	Glycosuria, gm.	Remarks.
1914.					
May 19	48.6	3.0	Subcutaneous injection	0	Normal dog.
June 2	46.4	5.0	Subcutaneous injection	0	
8	..	6.0	Subcutaneous injection	0	
26	41.8	7.0	Subcutaneous injection	Faint	
July 8	40.0	7.0	Stomach tube	0	
13	39.2	9.0	Stomach tube	0	
Dec. 13	39.4	9.0	Subcutaneous injection	0.6	
17	Removed processus lienalis of pancreas weighing 26.6 gm.				
1915.					
June 2	38.0	4.0	Subcutaneous injection	0.52	
11	38.0	2.0	Subcutaneous injection	Faint	
18	36.4	4.0	Stomach tube	0.76	
30	39.2	4.0	Subcutaneous injection	Faint	In the first twenty-four hours after the injection 344 c.c. urine, faint glycosuria; in the second twenty-four hours after injection (fasting), 2537 c.c. urine, sugar-free.
1916.					
Feb. 17	45.0	12.0	Stomach tube	0.17	1 hour after feeding.
				1.22	2 hours after feeding.
				1.31	3 hours after feeding.
				0.25	4 hours after feeding.
				Faint	5½ hours after feeding.
Mar. 7	Removed pancreas tissue weighing 12.7 gm.				
May 8	45.0	12.0	Stomach tube	1.72	
16	Removed pancreas tissue weighing 6.81 gm.				
June 5	..	12.0	Stomach tube	1.58	4½ hours after feeding.
				0.52	6½ hours after feeding.
				0	24 hours after feeding.
20	Removed pancreas tissue weighing 9.45 gm.				
July 27	35.5	12.0	Stomach tube	7.58	5½ hours after feeding.
				9.59	20 hours after feeding.
					49.1 gm. sugar lost in feces.

The dog at first did not thrive in confinement and the weight gradually fell from 48.6 to 39.4 kilos. This difference was sufficient to raise the ratio of pancreas weight to body weight appreciably and would have increased the tolerance of a diabetic dog markedly. The complete assimilation of 9 gm. of glucose per kilo by stomach tube on July 13 and the excretion of 0.6 gm. from the same dose subcutaneously on December 13 represented about the average tolerance and indicated no rise of tolerance in the normal animal from diminution of body weight.

After removal of the splenic process of the pancreas on December 17 it will be observed that the tolerance was lowered so that faint glycosuria resulted from as little as 2 gm. of glucose per kilogram subcutaneously and an appreciable excretion from 4 gm. per kilo either subcutaneously or by stomach tube. Attention may be called incidentally to the fact that in this and numerous other experiments abundant time was allowed to pass to exclude the effects of operative trauma and assure that the alteration of tolerance was permanent.

The diminution instead of increase of diuresis in such tests was sufficiently emphasized in a former publication and therefore the urine volumes are mostly omitted from these records. But it may

be repeated that when the tolerance is lowered so that small doses, with minimal osmotic influence, maintain hyperglycemia and slight glycosuria longer than in normal animals, the rule still holds that there is marked oliguria during this period and polyuria afterward, as noticed in connection with the experiment of June 30, 1915.

At the same time, as frequently mentioned elsewhere, this marked lowering of tolerance in a non-diabetic animal is apparent and not real, in the sense that it does not represent any limitation of the actual assimilative power. This was shown by the administration of 12 gm. of glucose per kilo on February 17, 1916, when the absolute dose was 540 gm. and the total excretion 3 gm., *i. e.*, only the barest trifle more than a normal dog eliminates from the same dose. Higher dosage would have been the only requisite to obtain still higher assimilation.

Successive portions of pancreas were then removed, at first without any apparent effect upon the assimilation of the 12 gm. dose of glucose. Finally the operation of June 20, 1916, brought the animal close to the verge of diabetes. Active diabetes might in fact have been present except for the low body weight of 35 kilos at that time, due to impaired digestion and diarrhea. In previous tests the feces had been free from sugar, but on July 27 there was diarrhea, with loss of 49.1 gm. glucose. Nevertheless, the sharp change from the former condition is seen in the excretion of over 17 gm. glucose in the urine.

The dog's general health prevented continuing the tests into later stages of diabetes. The principal point of the experiment was that a large dog, with a small endowment of pancreas in proportion to body weight, possessed the average glucose tolerance of the species, and this tolerance declined no more than usual with the removal of successive portions of pancreas.

TABLE VI.—DOG B2-61.

Date.	Glucose dosage, gm. per kgm.	Weight, kgm.	Administration.	Glycosuria, gm.	Remarks.
1914.					
May 27	8.0	5.5	Subcutaneous injection	0.24	Normal dog.
June 2	6.0	5.5	Subcutaneous injection	Faint	
8	5.0	5.6	Subcutaneous injection	0	
26	7.0	6.0	Subcutaneous injection	0	
July 8	8.0	6.5	Subcutaneous injection	Faint	
13	8.0	6.1	Stomach tube	0.10	
17	9.0	6.4	Subcutaneous injection	0.30	
30	7.0	6.5	Stomach tube	Faint	
Aug. 12	8.0	6.3	Stomach tube	0	
Nov. 9	8.0	6.0	Subcutaneous injection	0.20	
13	Removed tissue weighing 11.74 gm., about two-thirds of pancreas.				
1915.					
June 2	3.0	..	Subcutaneous injection	Slight	3½ hrs. after injection.
				Slight	9 hrs. after injection.
				0	22 hrs. after injection.
11	1.5	6.7	Subcutaneous injection	Faint	5 hrs. after injection.
				0	7 hrs. after injection.
18	3.0	6.9	Stomach tube	0.32	3 hrs. after feeding.
				0	10½ hrs. after feeding.
30	4.0	6.6	Subcutaneous injection	Faint	18 hrs. after injection.

Remarks on Dog B2–61.

Several experiments were undertaken with much smaller animals than this, but they were not strong enough to go through the repeated tests and operations and resist distemper and other accidents. This animal was a small black mongrel, fat when received at a weight of 5.5 kilos, so that 5 kilos was assumed as the normal weight for reckoning purposes throughout. She became more obese under the conditions of cage life. According to general rules a high ratio of pancreas weight to body weight was to be anticipated and the actual finding was that this animal possessed 3.75 gm. of pancreas tissue per kilogram.

The glucose tests in the normal state indicated a slightly lower apparent tolerance both subcutaneously and by stomach tube than in Dog 260.

November 13, 1914, the two processes, representing about two-thirds of the pancreas, were removed, leaving most of the body of the gland in place. The tolerance was lowered so that faint glycosuria resulted from as little as 1.5 gm. of glucose per kilo subcutaneously on June 11, 1915.

Accordingly a small dog with a high ratio of pancreas to body weight has no higher glucose tolerance than a large dog, and there is no greater "margin of safety," as judged by the lowering of the apparent tolerance by removal of pancreatic tissue. It was already concluded from the compilation of records in paper I of Series I that there is no uniform difference, outside of the limits of error, in the proportion of pancreatic tissue which must be removed to produce diabetes in large and small dogs.

Remarks on Table 7.

Instead of single dogs with removal of successive portions of pancreas this table is made up of different dogs possessing different portions of the gland. The "Remarks" column is occupied mostly with the fractions of pancreas remaining. Though the body weights frequently varied the original weight in each instance is used as the standard for dosage in all tests.

The normal dog No. B2–40 tolerated 10 gm. glucose per kilo subcutaneously when first received. The animal refused all food in the strange surroundings, so that from January 28 to February 3 the weight fell from 11.7 to 10.6 kilos. A smaller glucose injection was then given (6.7 gm. per kilo on the original 11.7 kilo weight), with the result of high glycosuria in a very small urine volume. A distinction must be made between this "hunger glycosuria" and the effect of simple changes of weight. A normal dog is unchanged in tolerance by changes of weight, but is subject to this transitory glycosuria or hyperglycemia on receiving carbohydrate

after long fasting or scanty diet. The true tolerance of a diabetic animal rises when the weight is reduced even by fasting, but in mild cases the sudden giving of carbohydrate after fasting or even after protein-fat diet often causes a transitory glycosuria like that of normal animals, but heavier.[4]

TABLE VII.

Dog No.	Date.	Weight, kgm.	Glucose dosage, gm. per kgm.	Administration.	Glycosuria, gm.	Remarks.
B2-40	Jan. 28	11.7	10.0	Subcutaneous injection	Faint	Normal dog.
	Feb. 3	10.6	6.7	Subcutaneous injection	3.8% in 7 c.c. urine	Weight lost by refusal of food.
C3-91	May 8	18.0	12.0	Stomach tube	1.1	Normal dog.
B2-59	19	41.8	3.0	Subcutaneous injection	0	Normal dog.
	June 2	40.0	5.0	Subcutaneous injection	0	
	8	..	6.0	Subcutaneous injection	0	
	26	40.0	7.0	Subcutaneous injection	Faint	
	July 7	39.1	9.0	Stomach tube	0.36	
	13	38.2	7.0	Stomach tube	0.76	
	30	42.5	5.0	Stomach tube	0	
B2-62	June 2	7.7	3.0	Subcutaneous injection	Slight	Only uncinate process present one-third to one-fourth of pancreas.
	8	7.6	2.0	Subcutaneous injection	Faint	
	26	8.3	4.0	Subcutaneous injection	0	
	July 2	..	4.0	Stomach tube	0	
	7	8.3	6.0	Stomach tube	0	
	13	8.4	7.0	Stomach tube	0	
	17	9.2	8.0	Stomach tube	Slight	
	30	9.5	8.0	Stomach tube	Slight	
	Nov. 24	Removed pancreatic tissue weighing 0.2 gm.				
	Mar. 30	..	9.0	Subcutaneous injection	0	
	April 8	..	8.0	Stomach tube	1.25	
B2-44	June 26	22.2	6.0	Subcutaneous injection	Faint	One-fourth to one-fifth of pancreas.
	July 2	..	6.0	Stomach tube	0	
	8	22.8	7.0	Subcutaneous injection	Faint	
	17	26.9	7.0	Stomach tube	0	
	30	21.0	9.0	Stomach tube	0	
B2-38	Feb. 10	12.1	1.0	Stomach tube	Faint	One-sixth of pancreas.
B2-57	July 8	11.3	3.0	Stomach tube	2.9	One-seventh of pancreas.
	13	..	2.0	Stomach tube	2.7	
B2-26	Dec. 30	19.0	2.0	Subcutaneous	0.23	One-ninth of pancreas; non-diabetic.
	Jan. 2	..	1.0	Subcutaneous	0	
	15	..	1.2	Subcutaneous	0.15	
B2-71	June 26	13.1	3.0	Subcutaneous	0	One-ninth of pancreas, non-diabetic.
	July 8	13.3	4.0	Subcutaneous	0	
	17	13.3	6.0	Subcutaneous	Faint	
	30	13.5	4.0	Stomach tube	0	
	Aug. 12	13.0	6.0	Stomach tube	Faint	
	Nov. 19	11.9	6.0	Subcutaneous	Faint	
B2-10	Jan. 2	7.0	2.0	Subcutaneous	Faint	One-tenth of pancreas.
	5	..	1.5	Subcutaneous	0.15	Diabetes prevented first by cachexia and later by hypertrophy of pancreas remnant.
	9	..	0.9	Subcutaneous	0	
	April 3	6.0	1.2	Subcutaneous	0	
	20	7.0	1.8	Subcutaneous	Faint	
	27	6.3	1.8	Subcutaneous	Faint	
	July 7	10.7	2.0	Stomach tube	1.0	
B2-31	April 27	9.6 (11.1)	.. 1.0	Stomach tube	1.50	One-eighth to one-ninth of pancreas, diabetic.
C3-13	June 30	13.5	4.0	Subcutaneous injection	12.7	One-eleventh of pancreas, diabetic.

Dogs C3–91 and B2–59 furnish examples of the normal tolerance in large animals, one 18 and the other above 40 kilos in weight.

Dogs B2–62 and B2–44 were examples of exceptionally high tolerance after removal of a considerable part of the pancreas. The former animal was small and the latter large, so the difference did not pertain to size. The ordinary glycosuria of such animals is so slight that it might easily be stopped by any slight cause, and the question whether the obstacle in these cases may have been a slight renal impermeability was not investigated.

Dog B2–38, possessing one-sixth of the pancreas, showed faint glycosuria from 1 gm. glucose per kilo by stomach tube.

Dog B2–57, possessing one-seventh of the pancreas, excreted 2.9 and 2.7 gm. glucose respectively from 3 and 2 gm. per kilo by stomach tube.

Dog. B2–26, non-diabetic with one-ninth of the pancreas, excreted titratable quantities of glucose from 2 gm. and from 1.2 gm. per kilo, but none from 1 gm. per kilo, subcutaneously.

Dog B2–71, also non-diabetic, with one-ninth of the pancreas, showed a contrasting behavior, in that glycosuria was absent with 4 gm. and only faint with 6 gm. per kilo, both subcutaneously and by stomach tube. Attention may be called incidentally to the usual close parallelism between the results of administration subcutaneously and by stomach tube in this and other experiments.

Dog B2–10 had been left with only one-tenth of the pancreas, but was non-diabetic at the time of the tests, because illness and emaciation following operation had allowed time for successful hypertrophy of the pancreas remnant. The apparent tolerance subcutaneously lay between 1.2 and 1.8 gm. per kilo, while 2 gm. per kilo by stomach tube caused an excretion of 1 gm. of glucose.

Dog B2–31 was diabetic, with a remnant between one-eighth and one-ninth of the pancreas, but was long kept aglycosuric by a limited protein-fat diet at a reduced body weight. During this period of latent diabetes the animal, at a weight of 9.6 kilos, was given by stomach tube 11 gm. glucose, which was 1 gm. per kilo on the normal weight of 11 kilos. An excretion of 1.5 gm. glucose resulted.

Dog C3–13, diabetic, with one-eleventh of the pancreas and similarly kept free from glycosuria on protein-fat diet, received 52 gm. glucose, or 4 gm. per kilo, subcutaneously, and excreted 12.7 gm.

The last two animals illustrate diabetic characteristics, in that even in latent diabetes small doses of sugar are likely to cause an appreciable excretion, which increases markedly with the dose. As long as the diabetes is kept under control the animal evidently possesses enough of the internal pancreatic secretion to utilize the greater part of any single dose; but with repetition of doses or

any other cause of glycosuria the loss of sugar increases, even to the point where the total quantity administered is eliminated. Examples of this behavior during active diabetes have been previously given,[6] so that they need not be repeated here.

Any gradual character of the decline of apparent tolerance should not cause confusion as to the sharpness of the point at which the reduction of the true tolerance begins. As previously mentioned, this point may be so sharp that the removal of one-tenth of a gram of pancreatic tissue makes the difference. Before the removal of this tenth the excretion from any dosage of glucose given by stomach or subcutaneously is relatively trivial, and the maintenance of even a slight glycosuria permanently (or continuously through any long period of time) is absolutely impossible. After the removal of the tenth of a gram of tissue not only is glycosuria greater, but it can be maintained indefinitely and tends to increase. This is the condition which has always been known clinically as diabetes.

This discussion is based upon the older tests for glycosuria before the introduction of Benedict's new methods,[7] but the distinction is so vital as a boundary between uninterrupted health and a progressive fatal disease that it seems unlikely to be altered in principle by any improved chemical procedure.

Discussion. Certain quantitative deductions concerning the internal pancreatic function may be drawn from tests in the three degrees of assimilation which have long been recognized clinically.

1. *Normal Assimilation.* Here the tolerance corresponds to the average for individuals of the same species by all tests. Two factors are necessarily involved, namely, the supply of pancreatic hormone and the capacity of the body cells for storage, combustion or transformation. As the assimilation can always be overtaxed by sufficiently large doses of sugar the question may be raised as to which of these factors becomes deficient in the normal animal. It is rather surprising to find that the pancreatic element is not present in the superabundance ordinarily supposed, but that the removal of any significant fraction, such as a fourth or a third of the pancreas, causes a well-marked lowering of tolerance in the usual tests. In other words an excess of Langerhans tissue to serve as a mere "factor of safety" is not demonstrable; on the contrary there must be frequent occasions in ordinary life (such as the eating of a box of candy by a human individual), when the full power of this tissue must be exerted if the assimilation is to be strictly normal. It is therefore conceivable that the overtaxing of the pancreatic function is at least one element when the normal tolerance is

[6] Allen, F. M.: Glycosuria and Diabetes, 1913, Chapter VI.
[7] Benedict, S. R., and Osterberg, E.: Jour. Biol. Chem., 1918, xxxiv, 195.

exceeded, and that if the functional capacity of the pancreas could be augmented the sugar tolerance might be raised.

2. *Lowered Tolerance.* This is understood clinically as an abnormal tendence to hyperglycemia or glycosuria from carbohydrate, but short of the point of diabetes. It is to be interpreted as a slowing of the rate of sugar utilization by the cells. There are two conceivable conditions of such slowing. (*a*) With any reduction of pancreatic tissue or function the cells of the body may be chronically undersupplied with the hormone. Their ordinary metabolism may or may not be affected by such deficiency, but it becomes plainly evident under conditions of strain; (*b*) the other alternative requires the assumption that the function of the pancreatic islands is delicately adjusted to the immediate demands of metabolism and that an increased absorption of carbohydrate requires an increased flow of their secretion. Under this conception a reduced mass of pancreatic tissue might be fully adequate for ordinary metabolism, but unable to respond perfectly to carbohydrate excess. The two alternatives are not mutually exclusive and might both be true. The latter may seem *a priori* more plausible, but some evidence favors the former idea, namely, the supply of the immediate needs of carbohydrate metabolism by pancreatic hormone stored in the tissues. This evidence consists in Verzár's[8] observation that the respiratory quotient falls only gradually after total pancreatectomy, and that during the first few hours intravenously injected glucose still raises the quotient; and Hédon's[9] assertion that diabetes comes on more quickly after removal of a subcutaneous pancreatic graft which was barely large enough to keep a dog non-diabetic, than after removal of the entire pancreas of a normal dog. If these statements, especially the latter, could be proved beyond the possibility of errors from anesthesia, trauma, differences in nutritive state, etc., they would establish (1) that the pancreatic secretion is stored in the tissues, and (2) that the store of it is greater with a normal pancreas than with a small remnant of pancreas. Evidence for the other alternative will be considered in a subsequent review.

3. *Diabetes.* This has long been identified clinically by continuous or prolonged glycosuria and hyperglycemia. In the mildest diabetes such continuance may require a maximum ingestion of carbohydrate, but nevertheless there is a sharp distinction from any non-diabetic degree of lowered tolerance, in which such a continuance is impossible. A tendency to regard this classic distinction as fictitious has been manifested by some writers who are disposed theoretically to plot the curve of falling tolerance as a diagonal straight

[8] Verzár, F.: Biochem. Ztschr., 1912, xliv, 201; 1914, lxvi, 75. Verzár and v. Fejer, A.: Ibid., 1913, liii, 140.

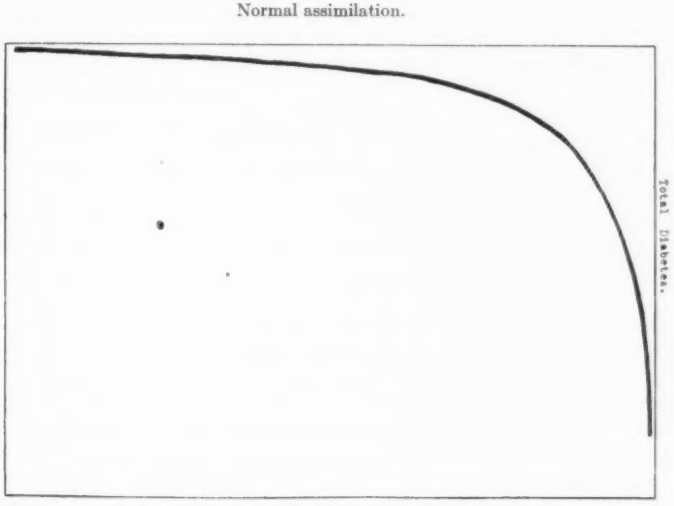
[9] Hédon, E.: Arch. internat. de physiol., 1913, xiii, 4.

line descending from the fully normal level to total diabetes. Thus an animal which had lost one-tenth of its pancreas would be one-tenth diabetic; one that had lost one-fourth of its pancreas would be one-fourth diabetic; one that had lost nine-tenths of its pancreas would be nine-tenths diabetic, etc. Several facts refute this theoretical conception and establish the strict clinical concept of diabetes. (*a*) From the standpoint of gross anatomy, even though all portions of the pancreas are practically equal in potency, the curve of falling tolerance is not a straight line. The importance of a given mass of tissue increases as the total remaining mass decreases. The point is reached where the removal of 1 or 2 grams has greater effect than the removal of 5 to 10 grams in the first place, and diabetes may finally result from the removal of as little as 0.1 gm. (*b*) There is an important distinction in the microscopic anatomy, for hydropic degeneration of islands never occurs in the non-diabetic state no matter how low the tolerance, while it always occurs in diabetes if the island function is sufficiently overtaxed. There is a narrow border condition in which slight vacuolation of islands may be present together with glycosuria or hyperglycemia on high carbohydrate feeding, and yet the vacuolation and the diabetes both clear up permanently; but this is merely the result of hypertrophy of the remnant or subsidence of inflammation, and therefore is not a real exception to the sharpness of the boundary. This is the basis of the tendency to aggravation which is characteristic of diabetes with excessive diets and the complete harmlessness of any excess in any state of lowered tolerance short of diabetes. (*c*) A third distinction is found in the so-called "paradoxial law" formerly stated by the writer.[10] The lowering of tolerance produced by removal of the greater portion of the pancreas is apparent rather than real. Only a trivial fraction of even the largest dose of sugar is excreted; the assimilation is merely slowed somewhat and remains actually unlimited. But after removal of about seven-eighths to nine-tenths of the pancreas a difference becomes evident, suddenly or gradually according to the form of the tests. The results of single doses of sugar are not infallible and special circumstances may cause a mildly diabetic animal to show an apparently better assimilation than one that is not quite diabetic. Nevertheless, there is a striking tendency to higher and longer hyperglycemia and glycosuria, which becomes greater the longer the excessive dosage is continued. The actual quantitative excretion is considerable, and with progress to the diabetes or removal of a few small fragments of pancreas it approaches more and more closely to the total quantity administered.

It may be said therefore that the curve of lowered tolerance resulting from the removal of successive portions of pancreas

[10] Allen, F. M.: Glycosuria and Diabetes, 1913, p. 67.

approximates a hyperbola. (See Figure.) Starting at the vertex of this curve one limb may be traced backward as a variable approaching the normal tolerance while the other limb descends as a variable approaching the limit of total diabetes.



Type of curve of reduction of carbohydrate assimilation by successive removal of portions of pancreas. (Ordinates, fractions of pancreas removed. Abscissæ, carbohydrate tolerance.)

Conclusions. 1. Dogs show an increased tendency to glycosuria from glucose given by stomach or subcutaneously when as little as a fourth or a third of the pancreas is removed. Apparently, therefore, the pancreas has little if any "margin of safety" from the standpoint of strictly normal metabolism, and there may be frequent occasions when its full endocrine function is needed for the purpose of fully normal assimilation. Quantities of sugar which exceed the normal assimilation may possibly be conceived as overtaxing the normal pancreatic function.

2. The internal secretory potency of different parts of the pancreas is equal, as far as such tests can determine; but the influence of a given mass of tissue increases as the total mass of remaining tissue decreases. The "margin of safety" of the pancreas with regard to diabetes is large, amounting in the dog to at least seven-eighths of the gland. The point at which diabetes begins is sharp and definite, according to three criteria: (*a*) An animal may be brought so close to the verge of diabetes that it is brought on by the removal of as little as 0.1 gm. additional tissue. (*b*) At this point a new histologic

phenomenon begins, namely, the hydropic degeneration of the islands described elsewhere, which is the basis of the characteristic aggravation of diabetes on excessive diets, while such excesses are harmless in any states of lowered tolerance short of diabetes. (*c*) The lowering of tolerance in any stage short of diabetes is only apparent, representing only a slight delay of assimilation while the actual capacity is unlimited, and the maintenance of continuous glycosuria through any long period of weeks or months is absolutely impossible by any quantity of sugar or any other food; but in diabetes the limit of assimilation is real and glycosuria progressively increases to the point of total excretion of the quantity administered. The curve of lowering of tolerance, with removal of successive portions of pancreas, is therefore approximately hyperbolic in form. Starting as a variable which descends by successive slight degrees below the level of normal tolerance, it turns at the vertex into a variable which approaches total diabetes as its limit.

3. Certain conceptions concerning the quantitative relations of the pancreatic hormone may be deduced as follows: It stands in some quantitative relation with the amount of carbohydrate metabolized, because a deficiency is revealed by moderate glucose dosage when only one-fourth of the pancreas is removed, and because of the above-mentioned proof that in diabetes the islands can be driven to destructive overfunction by carbohydrate excess and spared by regulation of diet. A more important quantitative relation is the minimum requirement of the body cells to prevent diabetes. When this minimum quantity of the hormone is present the organism retains its power to metabolize almost the whole of any glucose dosage that can be absorbed from the stomach or subcutaneous tissue, no matter how large or how long continued. When this minimum is reduced by only a trifle the phenomena of diabetes begin. With mild diabetes this deficit may be guarded against by restriction of carbohydrate. With more severe diabetes the total diet and body weight must be reduced. With still more severe diabetes the supply of hormone is inadequate for even the lowest metabolism and glycosuria is therefore uncontrollable even by fasting. As an example it may be assumed that a dog becomes diabetic with removal of between seven-eighths and nine-tenths of the pancreas, and in this condition requires maximal starch and sugar feeding to maintain glycosuria. Hopeless diabetes, uncontrollable by fasting, results (barring hypertrophy) when the remnant is about one-twentieth of the pancreas. The absolute difference between these fractions may be, for a fair-sized dog, perhaps 2 grams of pancreas tissue. Accordingly the difference between the demands of the highest possible carbohydrate metabolism and the demands of the lowest possible general metabolism amounts in such an animal to no more than the possible output of 2 grams of pancreatic tissue, only a small fraction of which consists of islands.

Such a calculation is of interest in animals when quantitative estimations can be made with approximate accuracy by operations. There is evidently a fallacy in the application to human patients, for it is impossible that the destruction of islands in human diabetes should always fall within the narrow limits mentioned. As a matter of fact, diabetes uncontrollable by fasting is very common in experimental animals and very rare in human cases. A possible explanation may be that one prominent feature of human cases is a functional defect which interferes with the internal secretory activity of the islands and at the same time renders them specially susceptible to damage from functional overstimulation. Such an explanation is supported by observations in other directions. One of these is the abundance of normal appearing islands in some clinical cases necessitating the assumption of a functional impairment. Another is the wide variation in the susceptibility of different human patients (especially the old and young) to degeneration of islands and corresponding decline of tolerance from dietary excess. At the same time it seems evident that a relatively small mass of normal island tissue can prevent diabetes, and the conclusion is therefore suggested that any positive means of augmenting the endocrine pancreatic function even by a little would give therapeutic results far surpassing those of the negative plan of sparing the function by diet.

DIAGNOSIS OF MYXEDEMA.[1]

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Myxedema is insidious in its onset, so that for a long period of time the characteristic clinical features may be absent, or, indeed, may not appear at all. The importance, however, of recognizing this disease is shown by two facts: (1) there is a sovereign remedy for its treatment, and (2) serious physical and mental developments ensue in long-overlooked cases, eventually reaching a stage in which there is an unsatisfactory response to appropriate measures.

It has been said that the disease is easily recognized when the characteristic features are present. This view, however, does not accord with the results of my experience and previous collective investigations. For example, out of 7 typical cases which have fallen under my care, and of which I have notes, 6 had gone unrecognized. Again, of 27 cases out of a total of 55 cases collected by me from American and Canadian literature and physicians, more especially those in charge of institutions for the care of the feeble-

[1] Read before the American Climatological and Clinical Association, June 18, 1920.

minded, since the year 1905, 20, or 74 per cent., had been overlooked by one or more physicians. This is a sorry commentary in view of the ease with which relief is afforded after recognition. In the remaining 28 cases of my series no reference to previous diagnosis was made. Writers upon the subject of myxedema fail to stress adequately failure to diagnose the disease on the part of practitioners of medicine, including clinicians of large caliber.

The first typical case that fell under my observation had been mistaken for chronic nephritis by one of the leading medical authorities of France and another equally famous American clinician. This occurred in 1892, at which time only 1 or 2 cases had been recorded in the literature, so that allowances could be made for failure to recognize the condition. It has, however, seemed to the writer to be inexcusable to find that this disease has been commonly overlooked by practitioners in recent years. A surprisingly small number of cases of myxedema have been reported in the past, but this fact need excite no surprise in view of the foregoing statement.

It would appear that the clinical picture of myxedema, despite the excellent delineation of the characteristic symptoms to be found in classic articles on the subject and in medical text-books and systems of medicine, has not been sufficiently impressed upon the mind of the profession. This is more specially true of cases in which, and these make up the majority, some of the diagnostic features are wanting. Efforts to stimulate interest in the subject, therefore, must be regarded as both timely and important.

In order to be in a position to appreciate the numerous and varied clinical features of myxedema, it must be remembered that an infiltration of all the anatomic systems of the body occurs in this disease, leading to an increase in the general bulk of the organism. Perhaps the most characteristic sign is a firm, inelastic thickening of the skin and subcutaneous fibrous connective tissue which does not pit on pressure. The dry, swollen skin of the face obliterates more or less completely the natural facial lineaments, so that in well-marked cases the patient seems to be wearing a mask, with broad, coarse, immobile features. The same dry, firm, inelastic, myxedematous infiltration of the skin of the extremities, and notably in the supraclavicular region, is to be observed.

The mucous membranes are also infiltrated and the teeth may become loosened. Chapman has emphasized a solid appearance of the conjunctiva as an early sign. The physiognomy "is stupid, dull and phlegmatic, and simulates imbecility." The tongue, lips and nose are thickened and the voice is peculiarly monotonous and has a "leathery tone, with curious nasal explosions at short intervals during speaking."

Thought and movement are slow and heavy, and while memory is good it is slow to respond. Retardation of psychomotor action is to be regarded as being quite characteristic of the disease. In

some instances headache is complained of, and there is marked irritability of temper, while in others hallucinations and delusions, tending finally toward dementia, supervene. Trophic changes of the hair and teeth occur. Destruction of the masticating apparatus is often noted. Baldness is a common symptom, and it usually presents a special distribution, the hair of the frontal region, nape of the neck and eyebrows being first shed. Albumin is commonly found in the urine, and occasionally tube casts as well. The temperature in myxedema is more or less subnormal as a rule. The thyroid is not palpable, not only on account of its atrophy but also owing to the presence of the thickened myxedematous tissues of the neck.

The foregoing text-book description of the symptomatology of myxedema in its typical form has been given on account of my firm conviction that the profession at large has an inadequate conception of this disease. It has been well said that "disease is a thing in itself and can be recognized as readily as flowers of the field or the faces of friends when these are seen often enough." The symptoms and signs of myxedema mentioned above, however, are so characteristic as to make individual recognition perfectly easy once a single typical case has been carefully scrutinized.

As stated elsewhere by the writer: "So commonly has chronic nephritis been mistaken for this complaint outside of institutions in which careful, thorough examinations are systematically conducted as to make fresh emphasis of the importance of its diagnosis highly desirable. Notwithstanding the fact that chronic Bright's disease and myxedema present few points of contact, clinically considered, but many of distinct dissimilarity, some of which are extremely striking, the latter is constantly and sadly being confused with the former disease."[2]

In my statistical inquiry, which covered the period from 1905 until July, 1919, or thirteen years, complications were recorded in 43 out of 55 cases, and of these urinary features, including albuminuria, with or without the presence of tube casts, were noted in 18, or 41.5 per cent. But though albuminuria was grouped with the complication in my series it is in reality a common symptom of myxedema, and if this fact were remembered the tendency to confound this disease with chronic nephritis would be markedly lessened. Edema of the extremities and of the face and legs was reported in 8 out of the 55 cases, or 14.5 per cent. This symptom is usually due either to an associated anemia or cardiac decompensation met with in advanced cases, and until the medical profession learns that such developments sometimes take place in myxedema, wrong diagnoses

[2] Myxedema and Cretinism in the United States and Canada: A Statistical Study, Contributions to Medical and Biological Research, dedicated to Sir William Osler, in Honor of His Seventieth Birthday, July 12, 1919, by his Pupils and Coworkers, i, 283.

will continue to be made. It is to be recollected that an actual nephritis may be a late accompaniment of myxedema; it then results from a generalized arteriosclerosis, or may possibly be of toxic origin. The urinary findings usually met with in chronic sclerotic nephritis (small ring of albumin, long, narrow, hyaline tube casts) are observed. It has been my good fortune to witness the disappearance of an albuminuria as the result of thyroid feeding in a number of instances of myxedema which had been regarded as cases of chronic nephritis.

To avoid mistakes in diagnosis in well-characterized cases the physical characteristics, mental condition, the slow speech and leathery tone of voice, and changes that occur in the skin and subcutaneous connective tissue, must be especially noted. Recognition of the condition is based mainly on observation of skin and mucosa, and the fact that the myxedematous infiltration of the face and legs is harsh, inelastic, stiff edema does not pit on pressure, as is true of cardiac and renal dropsy.

There are a large number of cases of myxedema which might be termed rudimentary in type, on account of the feeble development of the principal diagnostic features. Many of these cases touch certain other diseases, and especially those of endocrine origin very closely. In a case which came under my care both tuberculosis and acromegaly were associated. The myxedematous element in this case had gone unrecognized. The combined use of pituitrin and extract thyroid was followed by a remarkable degree of improvement, especially as regards the evidences of myxedema which practically disappeared, while the previous use of pituitrin alone by the attending physician had proved futile. It has been repeatedly shown by such careful observers as Schiff, Magnus-Levy and others that feeding with pituitary gland is without effect in acromegaly.

In view of the marvellous improvement in myxedema treated with thyroid extract within a few weeks the detection of the combined affection when present is a matter of much practical importance. The association of these two conditions, myxedema and acromegaly, is not infrequent, and to add to the difficulties encountered in their discrimination they present certain points of great similarity. In both the skin is dry, the subcutaneous fibrous connective tissue thickened by overgrowth, the tongue enlarged, the mucous membranes, especially of the nose, soft palate and uvula thickened; in both there is irritability of temper, slowness of the mental processes and thick, difficult speech.

Certain obvious features, however, belong to each of these diseases alone when found to be combined. For example, the general bony enlargement with separation of the condyles, enlarged joints, the severe headaches, disturbances of vision, bilateral hemianopsia are dependent on the acromegaly, while the tendency to chilling, a subnormal temperature, miniature thyroid, malar flushes and

loss of hair, as well as a peculiarly distorted physiognomy (masked facies), belong to myxedema. When these two diseases are associated in a single case the acromegalous features may overshadow the less obvious myxedematous symptoms. For example, in my case of combined acromegaly and myxedema, marked headache, strabismus, enlarged bones and joints, decidedly prognathous lower jaw, collectively pointed to the former disease, and overshadowed the fewer symptoms of myxedema. The presence of constant chilly sensations, low temperature, the malar flushes, the large myxedematous pads, however, caused me to suspect associated myxedema and led to the employment of thyroid extract, with most gratifying results.

The history of my case clearly indicated that the symptoms of acromegaly preceded those of myxedema by several years, at least. This is most probably the usual order of development when these two affections coexist, the average age at which myxedema begins being much higher than for acromegaly. On the other hand, myxedema occurring before the growth of the bones is completed causes an arrest of ossification.

In this connection Dock has called attention to the necessity of tracing out all the relations in cases of ductless-gland disease. The fact remains to be stressed that in any polyglandular syndrome which presents symptoms of myxedema, however slight, it is advisable to apply the therapeutic test. Since promising results have been recently obtained by Webster and others from roentgen-ray treatment in early acromegaly a trial of that agent might be made in combined cases in which the symptoms afford merely a suspicion of this disease.

Another endocrine disease intimately related to myxedema along metabolic lines, and not infrequently associated with it, is exopthalmic goiter. We no longer regard these two affections as being diametrically opposed to one another in their pathogenesis and symptomatology. I have elsewhere discussed this relationship and pointed out that this knowledge has been largely the result of the experimental labors of Janney and Isaacson,[3] who have shown that similar metabolic disturbances may be present in both hyperthyroid and hypothyroid states, and also that the blood picture in exophthalmic goiter is practically identical with that of myxedema.

Janney[4] proposes to substitute the term "dysfunction" of the thyroid for the less adequate hyperthyroid explanation. In many cases of exophthalmic goiter symptoms of defective thyroid function are met with, and at present writing admit of explanation, more particularly the cutaneous and osseous changes, as well as hypoglycemia. On the other hand the moderate thyroid enlargement, exophthalmos, tremor, tachycardia, psychic stimulation and

[3] Arch. Int. Med., August, 1918, p. 761.
[4] Ibid., p. 187.

increased basal metabolism depend on hyperthyroidism, or at all events toxic substances due to an abnormal amount of thyroid hormones in the blood circulation.

As elsewhere stated these cases of exophthalmic goiter with marked deficiency symptoms must be recognized and distinguished from pure myxedema. In suspected cases, the diagnosis can be materially aided by the administration of small doses of thyroid extract. Bertine[5] cites recent cases in which hyperthyroid and hypothyroid symptoms were combined in the same person. While it would lead too far afield to recite individual cases of associated myxedema and Graves's disease, it should be recollected that in these combined cases the symptoms of the former disease are those belonging to mild types, as a rule, hence less obvious than in the typical cases.

Several varieties of myxedema have been described. Formerly two main groups were recognized, acute and chronic, but more recently the former has been recognized as tetany. Following operations, and in exophthalmic goiter, however, myxedema may develop acutely without assignable cause. Postoperative myxedema, however, is rare, only 7 cases having been reported to date in Canada and the United States. Osler[6] reported a remarkable case of rapid development and fatal termination to the American Neurological Association in 1898.

There are many cases of incomplete symptomatic development in which we are justified in suspecting the disease in question and should not fail to cautiously carry out thyroid treatment with a view to confirming our suspicions. These incomplete forms have been discussed by Hertoghe,[7] Buschan, Pel, Osborne and others. Their course and progress vary greatly.

The symptoms in these instances of mild chronic hypothyroidism are dependent on the constant lesion of myxedema, namely, infiltration, which, however, may be slight and more or less localized. According to my observation certain features are common to all of them, *e. g.*, abnormally low temperature, an inclination to chilly sensations, a dry, often yellowish, firm, inelastic skin, disinclination to perspiration, tendency to an increase of the general bulk of the body, irritability of temper, lack of mobility of features, physiognomy dull and uninteresting and a thickened condition of the skin and mucous membranes, which is partial, often strictly circumscribed, rather than general, and most commonly affecting the lips, nose, cheeks and tongue. In isolated cases a variety of less obvious symptom groups are to be considered according to the sex and associated conditions before an assured diagnosis or a probable recognition even is possible.

[5] Medical Record, New York, 1916, xc, 895.
[6] Dock, in Modern Medicine, Osler and McCrae, iv, 895.
[7] Medical Record, New York, 1914.

The importance of a closer, more thorough study of these mild forms of the disease needs to be emphasized, in view of what is known of the effects of thyroid want. While our knowledge of the function of the thyroid is still incomplete it is indisputable that the cells of the body cannot attain to a perfect morphologic state when the secretion of this gland is markedly diminished. Again, as Hertoghe has pointed out, "When the thyroid supply is scarce the carrying away of cellular waste matter is slow and incomplete—mucin, fat and other principles accumulate on the spot and there form an infiltration and edema of a special kind—hard, non-depressible."

Among these mild types the following case from my records is a not rare one:

C. A. H., female, aged forty years, active housekeeper. Family history entirely negative. Had had childish diseases, including diphtheria and scarlatina, and at the age of twenty-six typhoid fever. The patient is married, has one child, aged fourteen years; menstruation has always been very painful and profuse. For three months or more before falling under my care she complained of symptoms of indigestion, cramp-like pains in the lower abdomen at frequent intervals, some distress in epigastrium immediately after food and nocturnal nausea on waking; appetite poor, flatulence, tendency to diarrhea; all symptoms aggravated during menstruation. The skin and mucous membranes exhibited a yellowish pallor, were slightly thickened, especially under the eyes, the lips and tongue, and there was some tenderness over the greater curvature of the stomach.

To these symptoms and signs were added those described above as belonging to all the various types in this group of mild forms. The use of thyroid extract was followed by a brilliant result, including normal, painless menstruation.

Another group of cases of so-called myxedema fruste, or incomplete myxedema, is characterized by irritability of temper, malar flush, apathy, neuralgias, headache, impairment of memory, tinnitus especially on lying down, slight deafness, slowness of the mental processes, undue susceptibility to cold, weak digestion, constipation, swelling of nasal mucosa, slight thickening of the skin and subcutaneous tissues often confined to certain regions of the body, early fatigue on exertion, and a moderate degree of anemia. The thyroid is usually smaller than the normal. It is to be recollected that in this variety cutaneous eruptions, such as eczema, psoriasis and urticaria, are present. In all suspicious cases I repeat it is strongly advised to make a cautious trial, with thyroid preparations as a diagnostic aid.

In one of my cases blepharitis was present and yielded to the specific remedy. In another, arthritic pains, affecting principally the knee-joints, were manifestly due to hypothyroidism; they yielded, though slowly, to small doses of thyroid. From the fore-

going examples it is clear that the specific cellular infiltrations in this disease may involve any of the body tissues, including the bones and cartilages.

In concluding it is hoped that progress resulting from continued study of these mild, imperfect forms of myxedema may tend to minimize the number of cases that escape the observation of the practitioner of medicine.

THE INFLUENCE OF PROTEIN FOOD ON INCREASED BLOOD-PRESSURE.[1]

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PROTEIN food has generally been regarded as having a definite influence on blood-pressure. A diet high in proteins has been supposed to raise blood-pressure, and *vice versa*. This principle has been widely applied in all diseases associated with hypertension, and, as a rule, a diet low in proteins, especially in meats, has been prescribed for patients exhibiting an increased arterial pressure.

It is disappointing to note on what very meager evidence the above ideas are based. Goodall[2] published some very convincing observations which showed that a distinct drop in blood-pressure occurred in cases of chronic interstitial nephritis on a low protein diet. Practically all other efforts in this direction, and they are very numerous, have confined themselves to general statements which either expressed an approval, or, in some instances, a disbelief, in this relation of blood-pressure to diet; however, the concrete evidence of carefully observed cases has been largely lacking.

The following blood-pressure determinations were made on patients who had been in bed for several days. This allowed the arterial tension to assume the lower level which mental and physical relaxation bring about. The manometer readings were made at approximately the same time every day. The patients were kept in bed continuously during this study. The long period over which some of the observations were carried out serves as a control for the fluctuations that may occur in the level of blood-pressure of individuals suffering with hypertension. During the periods of low-protein feeding the diets did not contain meat, meat products

[1] Read before the Association of American Physicians, May 4, 1920. The cases reported in this paper were observed at the Medical Clinic of the Johns Hopkins Hospital.

[2] Boston Med. and Surg. Jour., 1913, clxviii, 760.

(such as soups or gravies) or fish. These foods were taken in considerable amounts on the days of high protein feeding.

CASES 1, 2 and 3.—Neither a high nor a low protein diet have any remarkable effect upon the blood-pressure in a few days.

TABLE I.—Blood-pressure Observations on Case 1. (Chronic diffuse nephritis of slight degree.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.	Diet.	
	Systolic.	Diastolic.	Total N. P. N.	Protein, gm.	Character.
1	164	110	31.8	20	Low protein.
2	165	108	....	19	
3	162	106	....	20	
4	152	110	29.7	21	
5	156	96	....	166	High protein.
6	160	96	....	196	
7	175	110	....	201	
8	170	106	....	136	
9	150	106	37.0	150	

TABLE II.—Blood-pressure Observations on Case 2. (Female, aged fifty-six years, arteriosclerotic kidney of moderate degree; the urine contains a trace of albumin and a few fine granular casts; the urinary specific gravity varies between 1005 and 1015; 45 per cent. of phenolsulphonephthalein is excreted in two hours and ten minutes.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.	Diet.	
	Systolic.	Diastolic.	Total N. P. N.	Protein, gm.	Character.
1	175	118	21.2	11	Low protein.
2	155	114	....	10	
3	170	122	....	12	
4	156	120	25.4	10	
5	155	100	....	114	High protein.
6	166	104	....	107	
7	154	100	....	119	
8	184	70	....	131	
9	160	115	33.9	123	

TABLE III.—Blood-pressure Observations on Case 3. (Male, aged sixty-three years, essential hypertension; renal function normal.)

Day.	Blood-pressure.		Diet.	
	Systolic.	Diastolic.	Total calories.	Protein, gm.
1	204	124	2061	126
2	205	120	2055	125
3	...	...	2056	124
4	185	120	2063	126
5	218	138	2063	126
6	189	117	2212	78
7	166	110	2060	125
8	205	125	2061	126

CASE 4.—There is no notable change in the level of the arterial pressure on a high or a restricted protein intake, while the total number of calories is maintained at a constant level.

TABLE IV.—Blood-pressure Observations on Case 4. (Male, aged sixty-seven years. Secondary contracted kidney; at times a trace of albumin and a few hyalin and granular casts; a phthalein excretion of 25 per cent. in two hours and ten minutes; urea nitrogen, 34 mg. per 100 c.c. of blood; moderate arteriosclerosis.)

	Blood-pressure.		Diet.		
Day.	Systolic.	Diastolic.	Protein, gm.	Total calories.	Character.
1	190	120	91 (28)[3]	2344	Normal diet.
2	175	105	86 (19)	2498	
3	195	115	80 (28)	2501	
4	190	110	125 (69)	2065	High protein.
5	178	112	125 (74)	2065	
6	194	120	125 (75)	2065	
7	183	125	125 (76)	2065	
8	188	115	125 (76)	2065	
9	187	119	125 (69)	2065	
10	190	116	125 (79)	2065	
11	170	103	125 (64)	2065	
12	175	105	125 (80)	2065	
13	195	108	125 (78)	2065	
14	182	104	125 (68)	2065	
15	185	113	125 (76)	2065	
16	187	107	125 (80)	2065	
17	175	115	125 (72)	2065	
18	194	109	50 (18)	2065	Restricted protein.
19	181	109	50 (16)	2065	
20	178	100	50 (29)	2065	
21	173	103	50 (18)	2065	
22	209	114	50 (29)	2065	
23	178	105	50 (16)	2065	
24	203	115	50 (11)	2065	
25	188	117	50 (16)	2065	
26	173	106	50 (16)	2065	
27	183	110	50 (16)	2065	
28	182	110	50 (16)	2065	
29	182	110	50 (17)	2065	
30	190	115	50 (14)	2065	
31	206	125	50 (17)	2065	
32	190	125	50 (14)	2065	
33	210	120	50 (20)	2065	
34	195	115	50 (19)	2065	
35	201	115	50 (31)	2065	
36	185	115	50 (21)	2065	
37	205	110	50 (13)	2065	
38	205	105	50 (29)	2065	
39	202	112	50 (18)	2065	

[3] Figures in parentheses are the quantity of protein from meat or fish.

CASES 5 and 6.—The low protein diet is effective in producing a diminution in the blood urea nitrogen, but the blood-pressure remains unchanged.

TABLE V.—Blood-pressure Observations on Case 5. (Male, aged thirty-five years; secondary contracted kidney; albuminuria moderate; a few hyalin and fine granular casts; phthalein excretion, 21 per cent., in two hours and ten minutes; low fixed specific gravity of urine; albuminuric retinitis.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
1	210	140	61	97	..	Low protein.
2	...	...	..	..	15	
3	210	140	..	..	18	
4	...	...	41	70	20	
5	215	140	..	..	43	
6	...	...	..	..	53	100 gm. turkey added one day only.
7	210	135	..	..	28	
8	...	...	..	..	29	
9	...	...	..	..	25	
10	218	140	24	38	26	
11	...	...	..	..	25	
12	...	...	..	..	31	
13	210	145	..	..	44	
14	...	...	..	..	33	
15	220	145	..	..	29	
16	...	...	..	..	26	
17	210	140	..	..	24	
18	...	...	..	..	33	
19	213	145	15	22	28	
20	...	...	..	..	21	
21	200	139	..	32	65	Bread = 300 gm. added.
22	...	...	..	..	54	"
23	...	...	..	..	53	"
24	224	145	21	32	66	"
25	...	...	..	..	68	"
26	238	148	..	..	29	"
27	213	140	..	..	59	"

TABLE VI.—Blood-pressure Observations on Case 6. (Male, aged thirty-two years; an advanced case of arteriosclerotic kidney; the urine contains a trace of albumin and a few granular casts; the specific gravity is absolutely fixed at a level of 1010; only a trace of phthalein is excreted in two hours and ten minutes; Ambard's constant is 0.77; the blood-urea nitrogen is given in the table.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.	Diet.		
	Systolic.	Diastolic.	Urea N.	Total calories.	Protein, gm.	Character.
1	191	122	105	850	17	Low protein.
2	196	124	...	1571	15	
3	182	116	...	1626	16	
4	180	120	...	1721	16	
5	185	123	...	1755	19	
6	194	119	...	1778	20	
7	200	125	...	1838	20	
8	212	125	...	1687	20	
9	192	115	66	2396	82	

CASE 7.—A diet low or restricted in proteins is not accompanied by a drop in blood-pressure. An increase of the caloric value of the food results in no changes in the arterial tension.

TABLE VII.—Blood-pressure Observations on Case 7. (Male, aged forty-six years; secondary contracted kidney, with considerable impairment of renal function; phthalein, 26 per cent., in two hours and ten minutes; blood-urea nitrogen, after low protein diet, 27 mg. in 100 c.c.; Ambard's constant, 0.144; albuminuria, about 1 gm. per liter; many hyalin and granular casts.)

	Blood-pressure.		Diet.						
						Additions to diet.			
Day.	Systolic.	Diastolic.	Total calories.	Protein, gm.	Character.	Eggs, No.	Oatmeal, gm.	Milk, cream, c.c.	Meat, gm.
1	230	160	..	..	Ward diet				
2	219	155							
3	215	160							
4	219	161	..	..	Low protein				
5	235	158							
6	232	160							
7	230	140							
8	230	150	1676	22					
9	234	160	1722	17					
10	232	155	1937	22					
11	232	153	2038	25					
12	221	138	2116	34					
13	229	155	2274	36					
14	234	144	2136	38					
15	242	145	2299	47	....	3			
16	220	137	2302	49	....	3			
17	215	140	2300	48	....	3			
18	217	142	2110	39	....	2			
19	235	155	1552	17	Calories				
20	242	154	1513	17	Lowered				
21	222	153	1604	20					
22	231	145	1644	19					
23	224	145	1841	20					
24	228	145	1570	19					
25	224	155	2037	28	Calories				
26	228	145	2496	36	Raised				
27	218	135	2410	38					
28	220	138	2509	47	....	..	400	245	
29	229	150	2641	48	....	..	400	290	
30	232	145	2601	48	....	..	400	320	
31	218	145	2781	51	....	..	400	260	
32	214	147	2504	50	....	..	400	260	
33	220	145	2619	50	....	..	400	290	
34	224	145	2616	50	....	..	400	230	
35	218	143	2492	47	....	..	400	260	
36	220	142	2511	59	....	..	400	230	50
37	220	145	2669	63	....	..	400	280	50
38	224	152	2767	63	....	..	400	180	50
39	224	138	2761	74	....	..	400	280	100
40	218	138	2772	77	....	..	400	230	100
41	225	135	2718	65	....	..	400	230	50
42	230	148	2873	70	....	..	400	130	50
43	228	144	3026	73	....	..	400	310	100
44	214	145	2719	74	....	..	400	230	100
45	...	...	2819	75	....	..	200	260	100
46	232	145	2361	75	....	..	200	335	125
47	230	142	2819	75	....	..	200	260	150

CASE 8.—There is a tendency for a diminution of the blood-pressure with a diet very low in protein and low in caloric value.

TABLE VIII.—Blood-pressure Observations on Case 8. (Female, aged forty-one years; secondary contracted kidney, with marked impairment of renal function; phthalein, 10 per cent. in two hours and ten minutes; blood-urea nitrogen, 45 mg. in 100 c.c.; specific gravity of the urine fixed at a level of 1010; marked albuminuria and many hyalin and granular casts.)

	Blood-pressure.		Diet.		
Day.	Systolic.	Diastolic.	Protein, gm.	Total calories.	Character.
1	188	108	10	489	Low protein.
2	...	...	14	972	
3	190	110	14	898	
4	190	109	10	888	
5	175	100	11	664	
6	165	80	9	713	
7	165	80	9	897	
8	160	85	6	583	
9	155	84	9	766	
10	163	90	8	688	
11	150	85	8	623	
12	160	85	8	538	
13	164	95	8	714	
14	...	...	8	561	
15	185	115	7	608	

CASE 9.—A distinct drop in the blood-pressure occurs with the initial period of low protein diet. The original height of the blood-pressure is promptly resumed when 250 gm. of meat are added to the diet. When the meat is discontinued and the low protein diet substituted the blood-pressure does not fall to the previous level which the first period of low protein feeding produced.

TABLE IX.—Blood-pressure Observations on Case 9. (Male, aged twenty-five years; secondary contracted kidney, with marked impairment of renal function; phthalein, 10 per cent. in two hours and ten minutes; blood-urea nitrogen as in the table; Ambard's constant,, 0.63; albuminuria marked; hyaline and granular casts.)

	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
Day.	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
1	165	120	..	...	..	"Ward, light."
2	165	120				
3	160	90				
4	166	100				
5	165	103				
6	160	100	99	125		
7	163	100	..	...	5	Low protein.
8	165	100	..	...	7	
9	160	105	..	...	4	
10	150	98	..	...	6	
11	146	97	..	...	8	
12	145	95	..	...	10	
13	125	88	126	145	9	
14	125	85	..	...	8	
15	125	90	..	...	10	
16	125	90	..	...	9	
17	130	80	..	...	11	
18	125	85	..	...	10	
19	125	85	..	...	9	
20	127	82	103	123	9	
21	130	85	..	...	11	

TABLE IX (Continued).

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
22	135	88	..	...	13	
23	135	88	..	...	15	
24	145	98	..	...	15	
25	145	103	..	...	12	
26	160	103	..	...	14	
27	165	112	..	...	13	
28	150	103	49	66	17	
29	140	95	..	...	10	
30	137	88	..	...	16	
31	135	90	..	...	12	
32	140	97	..	...	13	
33	143	98	..	...	15	
34	145	98	32	...	13	
35	147	100	..	...	68	250 gm. meat added
36	155	105	..	...	75	
37	169	122	..	...	52	
38	170	120	64	...	72	
39	170	120	..	...	73	
40	170	120	..	...	52	
41	170	120	..	...	52	
42	168	115	..	...	84	
43	169	118	..	...	47	
44	167	116	..	...	26	
45	150	105	63	95	53	
46	155	107	..	...	75	
47	163	107	..	...	74	
48	170	110	..	...	71	
49	170	117	..	...	16	Meat discontinued.
50	170	113	..	...	16	
51	168	110	..	...	14	
52	170	115	55	79	17	
53	165	112	..	...	10	
54	169	122	..	...	18	
55	172	117	..	...	17	
56	168	120	..	...	18	
57	168	120	..	...	16	
58	173	117	..	...	18	
59	170	115	30	41	17	
60	170	116	..	...	19	
61	180	120	..	...	20	
62	...	...	..	...	21	
63	...	...	..	...	16	
64	175	120	..	...	14	
65	182	116	23	32	14	
66	180	116	..	...	18	
67	182	120	26	36	24	

Conclusions.—From these observations it would appear that it is exceptional for a low protein diet to diminish the blood-pressure or a high protein diet to raise it. Case 9, however, shows that this may occur. This patient was extremely ill, as the great impairment of renal function indicates, and was necessarily maintained in a state of undernutrition, since any attempts to increase the food resulted in uremic symptoms. However, even in this case a

second period of low protein feeding failed to bring the blood-pressure to the low level previously obtained.

The diminution of the waste products in the blood, as indicated by a lowering of the blood urea nitrogen, was without effect upon the blood-pressure. Changes in the caloric value of the diet, for a short time at least, did not influence the blood-pressure.

Discussion. The basis upon which the impression that a low protein diet reduces blood-pressure rests may possibly be found in the recent report of F. G. Benedict[4] and his collaborators. These investigators demonstrated that by underfeeding the blood-pressure of healthy, young, male adults could be distinctly reduced. This change was accompanied by various other phenomena, among them a secondary anemia. These facts furnish a suggestion as to the therapeutic application of diet to hypertension. A subcaloric mixed diet may be continued for a considerable period, probably with beneficial effect. If the health and strength of the patient are to be maintained it is advisable to regulate the amount of the diet according to the hemoglobin content of the blood. The hemoglobin percentage should not fall below 85 per cent. From the data given in the present communication it is evident that in most instances a low protein diet continued for a period of a few weeks is without effect upon the blood-pressure of cases of hypertension.

THE MANAGEMENT OF THE HEART IN PNEUMONIA.

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and

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Much of the experimental work which has been done in the past few years has tended to indicate that the importance generally attributed to the heart in the acute infections may have been overestimated in the past and that the causes of death in this disease lie largely outside the heart and that therefore treatment of whatever kind directed toward the heart may be of no avail.

This tendency appears to have followed largely after the conclusions of MacCallum, who found in experimental animals evidence tending to the impression that the heart is not essentially diseased in diphtheria.[3] MacCallum's conclusions were soon applied, at

[4] Human Vitality and Efficiency under Prolonged Restricted Diet, Carnegie Institution of Washington, Publication No. 280, 1919.

least in part, to pneumonia. The authors have, however, as yet to find any large list of carefully recorded microscopic examinations from a large number of cases which conclusively overthrow the old opinion of pathologists that in most of the acute infections an acute parenchymatous degeneration of the heart muscle is caused which, while of course not of a sufficient degree to immediately wipe out the possibility of contraction on the part of the heart muscle, so compromises this power that the organ is no longer able to "carry on" under the additional load above the normal which exists in most acute infectious diseases, and particularly in pneumonia.

The tendency of this viewpoint, which has naturally been developed chiefly by physiologists, pathologists, or at least men with but little actual bedside experience, has been toward a therapeutic nihilism which is becoming a very serious matter in the training of our young clinicians. We feel that the time has now come when this matter should be frankly considered more, or rather again, from the standpoint of the active clinician whose actual opportunity for observation in these matters is greater and whose interests are more from the standpoint of the humanitarian. Few men of large clinical experience are therapeutic nihilists, and it is a most unfortunate fact that so very many young practitioners are now being instructed largely along lines which cause them to go out into practice with the idea that the employment of drugs is useless, unscientific and almost unethical.

This tendency has been one of specially grave importance in the clinical management of pneumonia; this has appeared particularly to the authors who, during the past five years, have been thrown into intimate contact with very many young physicians in their ideas of this disease and its treatment.

We feel that the time is not only ripe but pressing when the clinician should have his say in regard to these matters and because he is no pessimist and because his experimental animals are human beings whom he is attempting to heal or render more comfortable is no argument that therefore his conclusions or viewpoints are unscientific or untenable.

We appear therefore with a brief for a therapy directed to aid the heart in pneumonia. This need we believe has not been sufficiently emphasized in modern teaching, or where it has been touched upon in treatment, the reference has often been buried in a mass of detailed recommendations, largely of what we believe to be of lesser importance, to such an extent that the position of the heart as of premier or almost single importance in the successful management of this disease has been, at times, lost sight of.

Few pathologists to our knowledge, even among those who fail to find sufficient evidence upon which to indict the heart for most fatal endings in pneumonia, but still admit the presence of acute degenerative changes in the heart muscle in this disease, though

usually of early and therefore not pronounced degree. This important agreement in observation interests us particularly, because it shows but a difference in degree of acknowledged responsibility of the heart in pneumonia between clinicians and other observers. W. W. Hamburger reported at the last meeting of the Association of American Physicians a group of carefully worked-up cases which fully substantiates our conclusions in this respect.

In March, 1919, it was the privilege of one of us to analyze, in association with Dr. Clarke, pathologist of the Ancon Hospital, five thousand protocols of cases dying of pneumonia in the A. E. F. In the study of this large material, which had been collected by all the pathologists then working with the army in France, certain points stood out which confirmed observations and suspicions in regard to the disease which had been formed from our previous much more limited but intimate personal pathologic and clinical experience with pneumonia. It is true that most of the cases which formed the particular basis of the Dijon study were instances of influenzal or postinfluenzal pneumonia, and that in several features these differed from what has been considered as typical of the usual broncho- and lobar types of pneumonia, but however the etiologic factors may have differed from the customary, the mechanical features of the disease and presumably the chemical also, are practically alike if not entirely identical.

One of the most outstanding and striking facts in connection with pneumonia is that fatal cases terminate almost invariably with what appears clinically as a cardiac death. In but very few instances from the whole material collected at Dijon could any other conclusion be drawn. Cases in which the involvement of the lung parenchyma was sufficient to justify the conclusion that death had ensued as the result of pulmonary deficiency were very few in number. This applied alike to both lobar and to the bronchial type of cases, and indeed, insofar as the heart itself is concerned it seems to make but little difference as to the type of the anatomic distribution of the consolidation. In general this seems also to hold true when one attempts to take into consideration the difficult question of the organism apparently responsible for the pulmonary disease in any instance.

None the less, degeneration of the kidney, very rarely sufficient to cause death was found in 712 instances of the 1651 cases investigated by Dr. Clarke. The less frequent complications of pneumonia, meningitis, sepsis, sinusitis, septic arthritis and so on are probable factors of serious consideration, but rarely when one studies the disease solely from its immediate terminal factors. Pneumonia from the standpoint of fatality, pathologically as well as clinically, may then be considered as a two-system disease; of the respiratory and the circulatory organs. When we consider the immediate termination alone it is practically always circulatory. The whole

battle in pneumonia, we would say, centers about two systems, the pulmonary and the circulatory. In but few cases is the termination other than through an apparent cardiac failure.

Analysis of these protocols showed us that the generally accepted clinical assumption is correct, namely, that the predominating cardiac lesion in pneumonia is an inflammation or degeneration of the heart muscle. It was present thus in 748 out of 1651 protocols.

We can readily see how the single-minded viewpoint of the pathologist might fail to see in many of the lesser degrees of degenerative lesions a sufficient cause for failure of the damaged organ. He, as a rule, is not given to evaluating, as the clinician is wont to do, the narrow margin of safety in the reserve physiology of the heart or the measure of added strain the organ may be called upon to undertake. As MacKenzie points out, heart failure is but exhaustion of the reserve force, and death appears immediately with exhaustion of the rest force. "It cannot be too strongly insisted upon that that process which we recognize as natural in a healthy individual is identical with the process occurring in an individual having some defect, whether the defect is due to disease of the heart itself or to other factors which embarrass the heart in its work."

In arriving at conclusions regarding the responsibility of right-heart failure for collapse and death in pneumonia the state of the heart muscle must be considered in connection with its inherent very low physiologic force (reserve and rest) as well as with the amount of unusual demand put upon this tissue during the course of pneumonia.

A fair measure of the normal reserve and rest force in the right heart may be arrived at from a consideration of the physiology of the lesser circulation and also the influence of peripheral strain which is the measure of left-heart strain on the pulmonary circulation. Wiggers's[5] work shows that the maximal pressure in the pulmonary system is 31.3 mm. Hg, the minimal 5.9 mm. Hg, the mean 19 mm. Hg, and the mechanical action of the respiratory movements contributes approximately 32 to 40 per cent. to the height of the maximal pressure and depresses the minimal pressure 10 to 20 per cent. "It appears that a change in total peripheral resistance is practically without influence on the pulmonary circuit when the change opposes the cardiac output in its effect."

From these facts the inference is justifiable that the reserve and rest force of the right heart is very small and its capacity for work in health or disease cannot be evaluated in terms of the left heart capacity. Clinically, unfortunately, the cardiac possibilities are usually taken as of the left heart. This is particularly untrue in pneumonia.

The amount of initial strain on the pulmonary circulation in pneumonia is indicated in part by the work of Gross[13] in a radiographic study of injected lungs from cases dying of pneumonia.

He demonstrated that varying degrees of vascular obliteration occur depending on the stage of pulmonary consolidation. In the stage of red hepatization there is a moderate preservation of the circulation, but there exist spaces in which vessels cannot be injected and even those injected are narrowed and compressed. In gray hepatization there is a general lack of injection and only the compressed large branches appear patent. These large branches ended abruptly and the whole area of gray hepatization presented a strikingly anemic appearance. The pathologic physiology of the obstructed pulmonary circulation lesions shown by Cross may be seen in such studies as those of Wiggers[3] with neutral oil injections: "Small amounts may be without effect on the mean arterial pressure, *but the pressure curves recorded from the right* ventricle showed typical signs that the right ventricle was contracting against an increased resistance.*" Larger doses produced a fall of mean arterial pressure; the pressure in the pulmonary artery increased and the effective venous pressure also was markedly increased.

These facts substantiate, we believe, the clinically accepted fact that every case of pneumonia begins with a strain on the right heart, and that this strain, in the light of known facts of the physiologic reserve in the part, is in amount that which justifies the conclusion that the *paramount factor in prognosis of all forms of pneumonia lies here, and that upon the ability of the right heart to resist the mechanical and toxic effects of the disease, mostly depends the fate of the patient.*

It would seem that much of the skepticism about the responsibility of the right heart insufficiency in pneumonia is attributable to the absence in many cases of outspoken cardiac distress. Stasis of any extent is an expression of a considerably increased blood mass which is contrary to Sandelowsky's[4] finding of a concentration of the blood in pneumonia. The already narrowed pulmonary circulation does not admit of total insufficiency to the point of extensive stasis without a sharp picture of collapse. Right-heart dilatation, unless immediately and vigorously treated is rapidly fatal, and it occurs before extensive gross or microscopic lesions of the heart have time to develop. The point we wish to make is that in pneumonia we are dealing with an acute initial maximal right heart strain plus a sharp narrowing of the factor of reserve in the pulmonary circulation superadded to a degenerated condition of the muscle consequent on the toxemia of the infection. Relative lesser circulatory insufficiency is accompanied by a severe general clinical picture bordering on or actual collapse, and diagnosis must therefore be in large part by inference and treatment to be of use, must be instituted to aid the work of the right heart from the beginning and in anticipation of its failure. This can be usually accomplished by the early and intelligent exhibition of digitalis.

* Italics ours.

We are, of course, fully aware that many instances of left heart failure occur in pneumonia. Its signs and symptoms are obvious and so striking that they can hardly escape the observation of any careful physician. We do not discuss them extensively here because of this fact and the still more important one that the treatment for the one condition suffices equally well for the other.

Believing, as we do, that heart failure in pneumonia is usually a matter of right-heart insufficiency the clinician must not then look for signs of left-heart disease or incompetence, but for the far more difficult signs and symptoms of early right-heart disease.

Up to within a few hours, or even moments of a right-heart failure, the sounds of the left heart may remain normal, the pulse-pressure may be within normal limits and the peripheral circulation well maintained.

What then are the signs and symptoms of impending right-heart failure? They may be entirely absent up to the very moment of failure, due to the very narrow margin of reserve force which the right heart possesses in health and much more so when it is diseased.

The signs of structural change in the heart, difficult as they may be to make out, may be seen in an increased diameter to the percussion surface. Failure to find this does not underwrite a competent heart. Fluoroscopy, however, will show early a right auricular dilatation. Of the patient's sensations, precordial distress, a sense of weakness and air hunger are important and significant signs. Jugular engorgement, indicating positive venous pressure, is an important sign, but this sign is also subject to intrathoracic pressure factors in the absence of true stasis. Among the most frequent signs of right-heart failure are unexplained increase in cyanosis, dyspnea and the appearance of substernal discomfort and edema of the lungs. A weakened second pulmonic tone is an important auscultatory sign. One must not expect peripheral edema and general cyanosis as in the usual signs of left heart incompetency.

We believe that small doses of digitalis at the outset of the infection enable the right heart to realize in the presence of an initial increased pulmonary pressure, a compensatory circulatory adjustment. Through this compensation at the onset the right heart in most instances is able to maintain an equilibrium. This appears to be so, as the greater number of cases of pneumonia survive throughout a considerable period of this and added strain. But we believe that every additional millimeter of strain added by factors other than those incidental to the vessels involved in the consolidation, counts—and counts very materially. In the discussion of these added factors the analysis of anoxemia offers itself as a means to that end.

From Hoover's work[10] we see that a fixed factor in oxygen unsaturation is a part of every case of pneumonic consolidation; that

is, the venous blood which flows through the involved area is returned to the aorta unchanged. This amount of anoxemia is a fixed factor and remains so until either there occurs obliteration of the vessels or resolution. Additional causes of increase in the unsaturation lies in shallow breathing, immobilization of the diaphragm and thorax and asynchronism—conditions which, in addition to their encroachment on the vital capacity of the lung, materially add to the right heart strain. The method of choice in combating these complications may be the oral insufflation apparatus of Meltzer,[12] which may supply a long-felt want in conditions requiring full artificial respiration. The subject of moisture in pneumonia is one intimately connected, we believe, with right-heart strain. In connecting moisture in the lung with right-heart strain, Mackenzie seems to stand almost alone. This rests upon the fact established originally by Welch that the cause of the high capillary pressure in the lung which explains the filtration, lies in a weakening of the left heart in the presence of a competent right heart. While this is true the essential factor behind the filtration is increased pulmonary pressure. Starling found that raising the pressure to 50 mm. for a few minutes was sufficient to cause an increase of loss by filtration of 10 to 15 per cent. of the blood volume. It appears therefore that fluctuations of pulmonary pressure in high values, even in the presence of a competent left heart, readily explain the appearance of moisture.

Bolton, working in Starling's laboratory,[8] has shown that stagnation of the blood alone, without either plethora or raised capillary pressure, may suffice to produce edema. It would seem, then, that regarding edema as an expression of variations in pulmonary pressure and as an indication for the use of means to relieve pressure increase is a rational inference. Moisture is a potent cause of increase in the oxygen unsaturation, and it is in such a state that the use of oxygen insufflation may be expected to materially reduce the cyanosis.

There are yet other very important problems which appear in the management of cases of pneumonia, which are important because of their relation to cardiac integrity. One of the very important of these is that of physical strain. Every clinician has noticed the very serious consequences which frequently follow when the patient is allowed to move about the bed at will, when he is allowed to sit up, and so on. Do all of us appreciate the very considerable physical strain to which we may subject the diseased heart when we insist on a complete and carefully detailed examination of our patient? If, as we have seen done, pneumonia cases are required to sit up in bed for demonstration to a class of students or to gratify the curiosity of the clinician at frequent intervals, the strain and exhaustion of our patient is very great. In instances in which question as to this statement has been raised we have asked the "doubting Thomas"

to count the pulse and to note the quality and rhythm of the patient's heart action before and after his examination and to particularly note increased dyspnea and cyanosis. For the sake of the heart the pneumonia case should be disturbed as little as possible. Meddling hydrotherapeutic measures, too frequent and too minute and too altogether careless examinations of the patient, have in our experience several times provoked an acute dilatation of the heart and exitus. We cannot insist too explicitly that the handling of the pneumonia patient must be as infrequent and as gentle as possible, all chiefly because of the heart. We have found, as probably have most other clinicians, that the use of the roentgen ray and fluoroscope is of tremendous assistance in the satisfactory study of cases of pneumonia, especially in the detection of complications, including sometimes dangerous degrees of right-heart dilatation. We found, moreover, that unless it was possible for the necessary manipulations to be carried out by carefully trained and thoroughly supervised teams of nurses and orderlies it was safer to forego the benefits of the method. Joslin, at Camp Devens Base Hospital in 1917 and 1918, permitted specially trained teams only to handle his cases and we very profitably copied his method at Camp Upton. When the pulse-rate was accelerated as a result of examination, in spite of its great utility, such examination was discontinued in all grave cases. Because of the heart, cases of pneumonia must be kept quiet and examined only as often as absolutely necessary, and then with great gentleness and as expeditiously as possible. Protection from mental strain is as important as that of physical strain in these cases. This is particularly so in excitable or irritable individuals, too much bustle in the ward, an excitable or talkative nurse or orderly, solicitous and unmanageable relatives are more than annoying factors in the care of patients suffering from pneumonia.

This care in avoidance of circulatory strain should be carried out during convalescence. It is our custom to insist that the patient shall not sit up in bed until seven days after the temperature has remained at normal or below for twenty-four hours. He is then permitted to sit up in bed and the heart action carefully noted—irregularities, weakness of the pulse, even a sharp exaggeration of the sinus rhythm is a signal for return to the resting position. If no appreciable effect on the heart is noticed and the case progresses at the end of another seven days the patient is allowed to sit up out of bed. Return to normal activity should not be permitted until pulse and patient have returned to former stability and vigor.

On the question of the use of digitalis in pneumonia most clinicians of experience appear to be in remarkable unanimity. Some question still exists as to when the drug should be given, the form most desirable, dosage and the manner of administration. It is advocated by many that it should not be employed unless signs of cardiac insufficiency appear; others believe, since digitalis is a drug from

which one does not expect immediate action, even when given in its most potent form and intravenously, that its use before the specific need develops is rational. Pharmacologists appear to differ on these points, although the recent work of Canby Robinson[15] and others indicates a digitalis effect within a few hours with oral doses of the drug. Some argue that the best effects of digitalis are gained on normal or relatively normal muscle and that when the muscle becomes extensively degenerated the response to digitalis is less satisfactory, a belief to which we subscribe. It would seem now that most clinicians, particularly those who have had an extended experience with the treatment of pneumonia, practically agree that to get the very best digitalis effect in the disease the administration of the drug should be instituted before its need is critical.

In our opinion the best effects are obtained when the drug is given early in the disease and before the heart shows any evidence of incompetency. In so doing the adjustment to the added right heart strains is aided, and when the full strain of the disease is thrown on the heart the muscle of which has degenerated to a greater or less degree, the organ is better prepared to resist the tendency to dilatation.

It is our usual custom to give digitalis at the moment that the diagnosis is made or even when it is highly supposititious. This routine early preparation has worked out beneficially in our hands and we have seen no untoward effects from this practice. S. S. Cohen's practice of the routine use of 5 minims of a good tincture by mouth three or four times a day is, in our opinion, sound and efficient therapy. We are not in the habit of giving excessively large doses except in instances in which we believe, or know beforehand, that the heart is crippled or subnormal. In such cases we ordinarily give the drug in doses of from 15 to 20 minims every two or three hours until the rate effect appears, the pulse becomes full, the muscle sound good and the apical thrust vigorous. If then the heart appears competent the dose is reduced to 5 minims every three hours or perhaps entirely discontinued. If signs of inordinate right-heart strain appear or incompetency develops the dose is immediately increased. At such times quickly acting forms of the drug may be preferable as digipuratum, given either orally or intravenously. This particular product has proved best in our experience, though in some cases digalen, digipoten and more recently digifolin have been used with apparently excellent results.

We have a distinct preference for the routine use of the tincture of digitalis, using always the physiologically tested tinctures. Our preference, doubtless, is for the reason that we have become more accustomed to this form of the drug and therefore perhaps use it more efficiently. We have, however, no quarrel with those who prefer the infusion, the fluid extract, the powdered leaves or perhaps

one of the newer forms of the drug. The choice and results are chiefly dependent on the familiarity of the user with his particularly familiar product.

The method of early maximum administration after the outline of Eggleston we believe is by all means the preferable procedure in cases in which the heart is known to be already seriously compromised by former or present disease, but we do not employ it otherwise for the reason that our clinical experience has contented us with a dosage and administration determined by digitalis effect rather than by any fixed rule.

Of recent years there has been a swing away from the practice of using strophanthus as a substitute for digitalis. This would seem to be chiefly due to the better standardization of digitalis products. Of late the use of strophanthus intravenously has had some vogue because of the frequent need of rapid effect not possible in the absence of a thoroughly satisfactory digitalis for intravenous therapy. Recent reports from the Rockefeller Institute show that because of the inferior glass in use as containers for strophanthus there is a fluctuation of H ion content in the solution and a sharp impairment in its potency results. But when a strophanthin of high potency is used, digitalis effects may be expected rapidly. While there are cases in which sudden dramatic failure of the heart occurs in pneumonia, we believe that the use of orally administered digitalis from the first will prevent sudden giving way in most cases, and under such conditions, the recently established fact that full digitalis effect may be early realized by stomach, much of the need for strophanthin intravenously is removed. It is questionable if strophanthin intravenously can be safely employed in already digitalized patients, we believe not.

We do not wish to be understood as demanding the use of digitalis in every case and every phase of pneumonia, but we think that we voice the general opinion of most practitioners when we say that its routine use is the more advisable practice, and cases in which we do not use it are the exception. Notwithstanding the general favorable impression as to its use there are some observers who think differently. So good an authority as Stuart Hart, in a recent contribution,[16] throws some doubt on the wisdom of its use in pneumonia, basing his opinions on an electrocardiographic study of a limited group of cases occurring in the influenza epidemic. Hart questions also the frequency of heart failure as a cause of death in the post-influenzal pneumonia in the 1918 epidemic.

Two facts struck us in his report which may bear comment: One is that in the small amount of material which came to autopsy the hearts showed "moderate degeneration" and that a criterion of favorable digitalis effect was expected and not realized in an appreciable slowing of the pulse. Regarding pulse slowing as an indication of favorable effects from digitalis, we have Cohn's finding[1] that

slowing of the pulse is not a primary effect of digitalis in therapeutic doses in hearts with normal sinus rhythm.

In our experience there are no other drugs which approach digitalis and strophanthus, particularly the former, in pneumonia. We have no others which are so much to be relied upon, though for emergency medication other drugs may be properly used. Of these we have found adrenalin one of the best, particularly in those instances in which the failure is associated with marked fall in general blood-pressure or when there is a persistent decrease in pulse-pressure, which we believe to be a most important indication that this catastrophe is perhaps impending. Except for temporary use in acute circulatory emergency we have seen no beneficial results following the administration of adrenalin either subcutaneously, intravenously or by stomach. Meltzer's work shows that this drug is at times a cause of edema of the lungs and hence not too safe a one for anything like routine use as a stimulant even if it may so act.

It is no longer fashionable to give strychnine as a "cardiac stimulant" in pneumonia, but many still so use it. Edmonds and others have shown to our entire satisfaction that strychnine is not a cardiac tonic or stimulant, but that it is a depressant. There are, however, instances in which we believe that we have seen it act favorably. This is in cases which have been digitalized and in which the irritability of the heart muscle seems to be defective. Given in such instances it has on several occasions in our experience apparently increased the effect of the digitalis. We have argued on purely speculative and clinical grounds that the drug may accentuate the irritability of the heart muscle.

Camphor, usually given in ether or in oil and administered subcutaneously, we believe to be of occasional efficacy when the heart requires frequent emergency stimulation. We do not believe that its effect endures long. For results it must be given in large dosage. It is not a drug to employ as a preparatory one in pneumonia, nor can it in any way replace digitalis preparations.

We use caffein with great frequency but in precisely the same case as camphor. It is for temporary and emergency stimulation only, not for persistent use. It may be given by mouth, subcutaneously, and particularly by rectum, or by mouth in the form of black coffee, all for the same identical purpose. It probably increases a tendency toward nervous irritability and the maniacal states.

Atropin is very frequently employed by us in the circulatory management of pneumonia. We use it as an adjuvant to digitalis or of the digitalis group of drugs when they have been perhaps pushed too far and block is threatened, and particularly in those instances in which an abnormally slow action of the heart occurs, as is frequently the case in the influenzal forms of the disease. It is very useful in cardiac collapse or acute dilatation, and

in many forms of arrhythmias, just which can usually be determined clinically only by experiment. It is especially valuable, however, in cases where, due to cardiac disturbances, pulmonary or glottic edema occurs or is threatened. In our opinion it should be prescribed with great care and its administration particularly carefully observed in instances of renal disease when fluid excretion is in question or when there are evidences of a tendency toward salt retention. It may also cause anaphylactic-like reactions in many patients, and is one of the drugs toward which idiosyncrasies are most commonly manifested; even when no such active tissue antipathy toward the drug is evident it may cause a considerable degree of discomfort in a good many cases, this is oftentimes a factor well worthy of consideration in so delicately balanced a clinical disease picture as pneumonia. It is rarely a drug which is to be long continued, but rather one for temporary use in certain complications and emergencies. Next to digitalis we find it the most frequently used by us in pneumonia.

The authors have no desire whatever to claim that every drug used with benefit in the treatment of pneumonia is used because of its favorable effect on the circulatory system; it will, however, doubtless be conceded that no drug having an unfavorable effect on the circulation is very widely advised in the treatment of any phase of pneumonia. Morphin and codein are drugs which we employ not only to quiet the cough in pneumonia, which is in itself often a very important thing to do in the conservation of the circulation, but also because used when indicated they decrease restlessness and emotional irritability, promote sleep and greatly ameliorate the sufferings of the patient, even if they do not, as some assume, act directly as a stimulant on the heart muscle.

Although venesection is less frequently resorted to now than was the custom, or shall we say the fashion, a few years back, there can be no doubt of its great utility in many cases and there are few clinicians who are unaware of this fact. It is, however, not by any means a measure of general utilization and it is applicable to but a small group of cases and as a rule but for a limited period of time. We shall attempt to indicate briefly those cases and periods as they have appeared to us. In plethoric, full-blooded patients, particularly in those fat or tending to obesity, venesection often gives great physical relief from the dyspnea and the distress of the labored breathing. It is still thought by some that if venesection be vigorously employed sufficiently early it may limit the extent of or may even abort an attack of pneumonia. Few, we believe, among modern clinicians can subscribe to any such optimism, but it appears advisable and beneficial when employed early in the course of some cases, and its indications are marked dyspnea, evidence of insufficiency of the right heart in plethoric individuals, excessive cyanosis as a part of the invasion, and particularly in cases of frank hyper-

tension. In profound early toxemia, with outspoken right-heart dilatation, hypotension should not be held as an absolute contra-indication. Venesection in the later stages of the disease is rarely advisable, except in those instances in which stasis from right-heart dilatation is unmistakable, and even when so indicated its result is problematical.

The amount of blood to be taken is governed by the degree of venous stasis and the reaction of the patient during the operation. As a rule it should be a substantial amount and one should lean to a generous blood-letting. When used as a means to relieve hypertension a sharp reduction in pressure or signs of cerebral anemia are the indications to stop. In low pulse-pressure states it has not been usually found an advisable procedure.

Spartein and many other drugs are frequently used for their cardiac effect in pneumonia. We do not discuss them here because of lack of personal experience. Each physician has learned for himself certain drugs and therapeutic measures which have proved successful in his hands; this is as it should be, but there are certain basic principles in the management of the heart in pneumonia which we believe should be always borne in mind together with a procedure best designed to meet such conditions.

A summary of these is: promotion of excretion, particularly by the bowel, of toxic material which probably contributes to the degenerative changes in the heart; the encouragement of active diuresis and the maintenance of an adequate water balance, both realized chiefly by the free use of water; the proper nourishment of the individual by means of a quickly combustible diet in which sugar and, in appropriate cases, alcoholic preparations may be advisedly used, and probably most important of all, the preparation of the heart for compensation to the initial strain and additional increments which are so strikingly a part of this disease.

We do not wish to convey the impression in this paper that we believe all cases of death in pneumonia occur as a result of cardiac disease or incompetence. We recognize fully death, as in toxic shock, with vasomotor paralysis as the most apparent symptom, cases which die from thrombosis, occasionally from acute renal defects and the like, but we do maintain that by far the most frequent immediate cause of death is from cardiac deficiency. We wish to restate our standpoint in the briefest possible way in the following conclusions:

CONCLUSIONS. 1. The most frequent immediate cause of death in all types of pneumonia is cardiac failure.

2. In by far the larger number of instances this failure is due to right-heart deficiencies.

3. This occurs because of the very limited muscle reserve capacity of the right heart, plus a myocardial degeneration, the result of toxemia.

4. The preparatory and emergency use chiefly of the digitalis group of drugs fortifies the heart against these tendencies.

5. Rest, properly timed venesection, and numerous other adjuvant measures are frequently of great therapeutic utility.

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THE ROLE OF THE ELECTROCARDIOGRAM IN PROGNOSIS: A STUDY LIMITED TO HEARTS UNDER SINUS CONTROL AND CONTRACTING AT AN APPROXIMATELY NORMAL RATE.*

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Aid in prognosis has long been sought through an interpretation of graphic records of heart-action currents. The value of a correct diagnosis as a basis for prognosis cannot be questioned. The nature of an arrhythmia can be demonstrated through a study of electrocardiographic curves. Yet the profession has been slow to avail itself of laboratory aids in the diagnosis and prognosis of irregularly beating hearts. Physicians have been even less liable to seek informa-

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tion in regard to those patients whose heart action is regular, especially if the heart-rate is not accelerated. Yet even in the latter group of hearts the electrocardiogram may furnish important information as to the state of the myocardium, information which may be essential to the forming of a correct prognosis. The object of the present paper is to attempt to assess the prognostic value of information derived from the study of electrocardiograms obtained from patients whose hearts were beating under the domination of the normal pacemaker and at a rate which was approximately normal.

Our records were collected in a general hospital in a large industrial city. The patients who were electrocardiographed were nearly all adults; the age incidence varied but the average was probably less high than would be found in many hospitals of the strictly charitable type. Patients were referred to the heart station from various departments in the hospital and by outside physicians, the services of the heart station being equally available to all. The following table indicates the source of the clinical material:

Total number of patients examined	780	
Medical service	480	61.5 per cent.
Gynecologic service	67	8.5 "
Dispensaries	49	6.2 "
Psychopathic service	29	3.7 "
Surgical service	11	1.4 "
Nose and throat service	4	0.5 "
Pediatric service	2	0.25 "
Genito-urinary service	2	0.25 "
Obstetric service	0	0.0 "
Unclassified as to service	80	10.0 "
Outside physicians	56	7.1 "
Number of cases excluded on account of ectopic origin of heart-beat or of rapid rate	220	
Available for purpose of present study	560	

The following abnormalities of the electrocardiogram have been considered.

1. Such distortions of the primary ventricular complex as are usually associated with conduction defects below the bifurcation of the main bundle.

2. Decreased amplitude of primary ventricular deflection as existing in the absence of other marked distortion of the electrocardiogram.

3. Prolonged P–R interval.

4. Invert T_1.

5. Alternation of heart action currents or of the strength of pulse-waves as registered upon the electrocardiographic plate by means of a special device.

We fully recognize the limitations imposed upon us by the nature of the material studied: in spite of these limitations we believe that the study has not been entirely fruitless. The method carried with

it at least one definite advantage—the elimination of the element of expectant attention.

I. Distortions of the primary ventricular complex have recently been the subject of careful study.

Oppenheimer and Rothschild[1] have called attention to the frequent association of certain definite peculiarities of the Q–R–S deflections with a group of clinical conditions—arteriosclerosis, coronary artery disease, syphilis—which are liable to be accompanied by degenerative changes in the heart muscle. These authors made postmortem studies of the hearts of 14 patients from whom electrocardiograms showing distortion of Q–R–S deflections of a special type had been obtained during life. Disseminated sclerosis which predominated in the endocardial and subendocardial layers was found in all but one; the prognosis in the presence of the described distortion of the electrocardiogram was believed to be grave.

The electrocardiogram which these authors believed associated characteristically with this type of myocardial involvement (which results in "disturbed intraventricular conduction") is described as follows:

1. Abnormal prolongation of the time interval of the Q–R–S group beyond the normal limit of 0.1 second.
2. Notching of the R wave.
3. Occasional low amplitude of the waves in all leads.
4. Absence of the typical diaphasic curves, with large T_1 waves, as found in experimental branch bundle block.[2]

Carter[2] concludes that "the presence of a predominant sclerosis of the terminal arborizations of the Purkinje system gives rise to electrocardiographic curves of low amplitude associated with a bizarre ventricular complex of a definite type. Curves of large amplitude, essentially diphasic, may justly be regarded from experimental evidence available, as indicative of a definite totally obstructive temporary or permanent lesion of one of the branches of the atrioventricular bundle. The presence of curves of low amplitude, so characteristic of a diffuse sclerosis, did not, however, preclude the existence of definitely localized focal lesions involving the main stem and its branches."

Robinson,[3] while accepting the conclusions of Oppenheimer and Rothschild[1] as applicable to a group of cases, has shown that a like distortion of the electrocardiogram may occur occasionally as an expression of what he believes to be temporary functional fatigue.

[1] Electrocardiographic Changes Associated with Myocardial Involvement, Jour. Am. Med. Assn., August 11, 1917, lxix, 429.

[2] Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med., September, 1918, xxii, 331.

[3] Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med., October, 1919, xxiv, 422.

Willius[4] states that arborization block is now generally accepted to indicate disease of the subendocardial myocardium and evidences serious functional cardiac disturbance.

Robinson's hypothesis added to the conclusions of Carter seems to be a fair summary of the present knowledge of block below the bundle of His.

A study of our records has convinced us that it is occasionally impossible to classify distortion of *Q–R–S* by the criteria of Oppenheimer and Rothschild.[1] Borderline records occur in which it is only possible to assign the block to a point below the main stem of the bundle. Furthermore, one cannot always prove that the block arises as the result of histologic lesion. Thus we have been unable to exclude the fatigue element in several of our cases, since some of our patients have presented themselves for examination but once. However, in no case have we noted a return to normal after the distortion of *Q–R–S*.

Our material consists of records of 19 patients, or a total of 3.4 per cent. of the patients with sinus rhythm: 60 per cent. of the patients were males. The average age incidence was fifty-seven; the youngest patient was thirty-five years old. Most of the patients presented the clinical picture of cardiorenal vascular disease. Syphilis is conspicuous by its absence. In only one case was a positive blood Wassermann obtained, this patient having an aortic insufficiency. In 10 cases the Wassermann was negative, as were history and evidence gained by physical examination. No Wassermanns were taken on any of the 8 remaining patients. In none of these was a clinical diagnosis of syphilis made, and in at least 2 of the 8 it is probable that the disease can be almost definitely excluded.

Measurement of serial plates showed that the width of the *Q–R–S* interval varied from time to time, as between 0.10 and 0.14 in one patient and 0.16 and 0.20 in another. However, widening, having once been established in a given case, the *Q–R–S* interval subsequently was never found to decrease below 0.1. The persistence of a given form of distortion, as established by an individual, has been striking at times. The following case is reported as illustrative:

W. H., male, aged seventy-three years. Admitted November 20, 1915, complaining of dizziness, weakness, dyspnea and swelling of the feet. The diagnosis was cardiorenal vascular disease. The patient remained under observation for four years. He died a cardiac death, December 11, 1919. No postmortem could be obtained. Electrocardiographic curves on admission showed subbifurcation block. The accompanying figures show that a change in contour of curves occurred during the first sixteen months, with but little change during the subsequent twenty-one months.

In regard to nearly all of the patients in this group there was

[4] Arborization Block, Arch. Int. Med., April, 1919, xxiii, 431.

sufficient clinical evidence to enable one to make a diagnosis of an underlying cardiosclerosis. That there are exceptions to this rule is shown by the following case:

H. J. M., male, aged fifty-seven years, clerk. Referred by an oculist for relief from headache: no sclerosis of retinal vessels; palpable vessels unusually soft for age; no symptoms referable to heart, which was apparently normal. Blood-pressure, 110–76. The arteriogram showed slight irregularity of the height of the pulse-waves but was otherwise normal; phthalein excretion (intravenous), 78 per cent. in one and a half hours; peridental infection; chronic sinusitis; pulmonary tuberculosis. Of two electrocardiograms taken at an interval of three weeks, both showed subbifurcation block.

The patient was markedly toxic during the period of observation. Unfortunately an opportunity has not arisen to examine him at a time when his heart muscle was carrying a lighter load. It is not impossible that this patient might subsequently have a return to normal contour of electrocardiogram.

Of our 19 patients, 9, or 40.7 per cent., are dead. Of these 6 lived less than four months after block was demonstrated. One died after a period of four years. Two are alive in whom the distortion was noted forty-five and forty-eight months ago.

We believe that the above statistics are confirmatory of the growing belief that a definite deformity of the *Q–R–S* deflections is often associated with extensive myocardial degeneration and that this finding should be sought for as part of routine in the case of patients showing evidence of cardiorenal vascular disease. Prognosis regarding this group of patients, can usually be made by an experienced clinician without laboratory help. However, the routine examination as carried on in a heart station may be of great value by indicating that certain patients should be referred to an internist before subjecting them to operation or discharging them from the hospital. In occasional cases electrocardiographic evidence of myocardial degeneration may occur in the absence of obvious signs of the disorder. It should be remembered that subbifurcation block may occur as a result of a temporary condition, such as overfatigue or toxemia. Consequently, in doubtful cases repeated observations may be essential.

II. Decreased amplitude of primary ventricular deflections may exist in the absence of other distortion of the form of electrocardiogram. There may be considerable variation in the height of the primary complexes in electrocardiograms of normal individuals. Thus, Lewis[5] found that if a series of curves be taken from a number of active students the minimum in the three leads was 1.5, 4 and 2 respectively, while the maximum was 10, 16.5 and 14 scale divisions. The average of 59 students examined was: Lead I, 5.16; Lead II,

[5] Clinical Electrocardiography, London, Shaw, 1913, p. 22–23.

10.32; Lead III, 6.61. Nevertheless, Lewis believes that considerable divergence from what is regarded as normal probably indicates that the heart is abnormal. White[6] states that "not infrequently one finds electrocardiographic evidence of a very weak myocardium in cases with a regular pulse. This is shown by one of two findings, a very low flat *T* wave (when one can rule out digitalis) and a small excursion of all waves in all leads." He concludes that very small deflections in all leads usually indicate a very weak myocardium. Frazer[7] noted, as a result of experimentally induced dilatation of rabbits' hearts, that a diminution of the size of all the waves of *Q–R–S* group was observed in degenerative conditions of the heart muscle. Oppenheimer and Rothschild[1] employed low amplitude of the primary ventricular complex as one of the criteria for recognizing the electrocardiogram which was associated with myocardial involvement with a bad prognosis.

In selecting a standard for sorting of our electrocardiograms, we have accepted ten scale divisions as the average normal. This has been done in full realization that each patient must establish his own normal and that any standard is therefore an artificial one. At most such deductions can be only inferential. Further sources of error may be due to instrumental defects and faulty technic. There was an occasional unexplained variant as illustrated in Fig. 4. In numerous instances the possibility of instrumental defect appears to have been excluded definitely by the fact that control electrocardiograms gave normal deflections. In a small group of patients there existed so striking a parallelism between lower amplitude and increasing myocardial insufficiency that the association could hardly have been accidental in all of them.

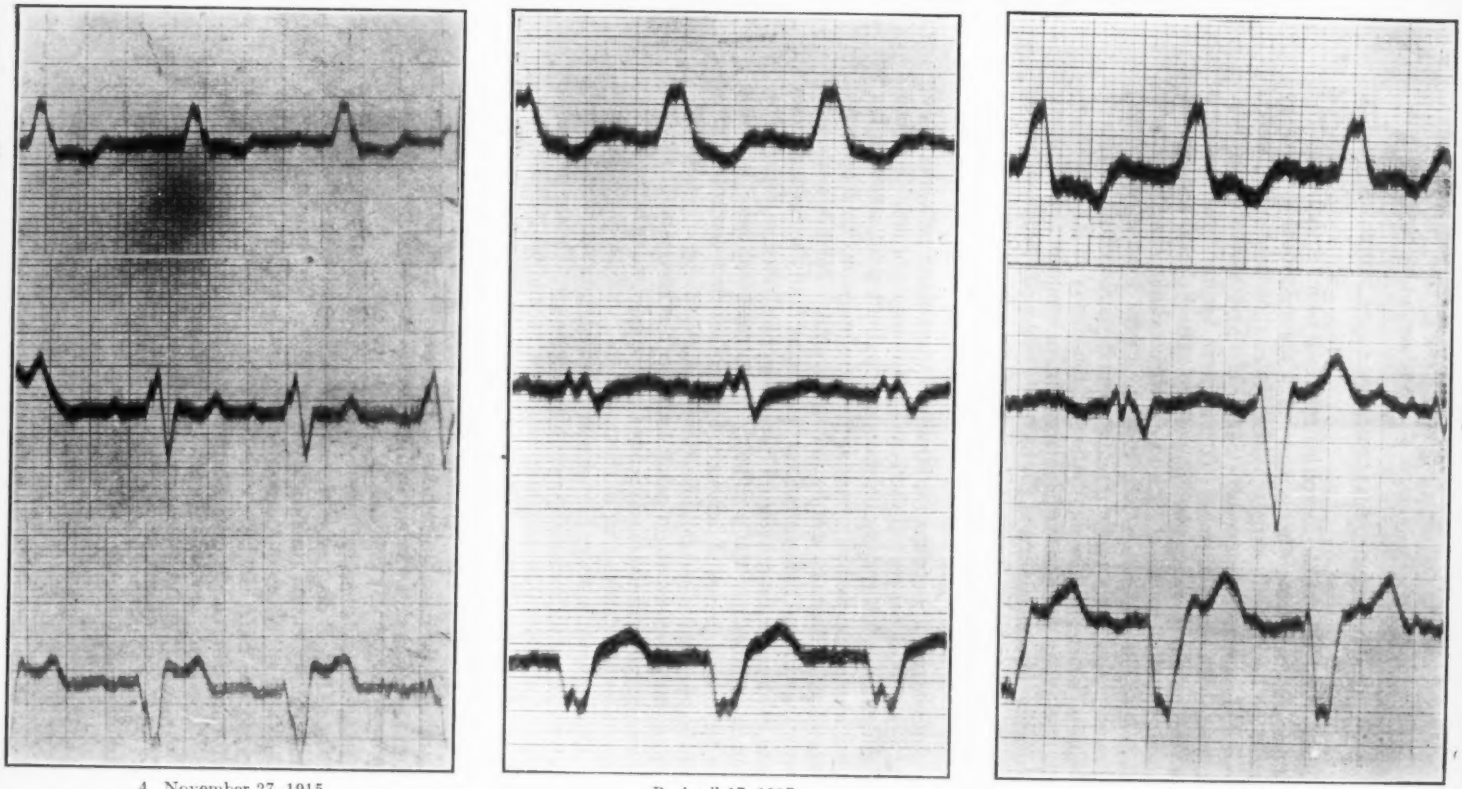
Of our patients, 46, or 5.8 per cent., showed constant or occasional low voltage in all leads; 56 per cent. were females. The age incidence differed widely. The mortality was relatively high: 17, or 36 per cent., are dead. Of the total deaths, 76 per cent. occurred in patients in the fifth decade.

The following case illustrates a changing amplitude exactly parallel to the clinical condition at the time the records were taken. It is believed that the electrocardiograms may be depended upon as each record was checked by control patients.

E. F. D., male, aged twenty-four years, admitted February 3, 1920. Clinical diagnosis; pericardial effusion; at first serous; later purulent. Effusion drained, April 14, 1920. The primary deflection of first electrocardiogram was eight scale divisions. This record was taken at a time when the patient was able to walk about, with apparent comfort. Subsequent curves taken at periods during

[6] Diagnostic Value of Electrocardiography of Hearts Beating Regularly, Med. Clinics of North America, January, 1920, iii, 1035.

[7] Changes in the Electrocardiograms Accompanying Experimental Changes in Rabbits' Hearts, Jour. Exper. Med., September, 1915, xxii, 292.



A. November 27, 1915. *B.* April 17, 1917. *C.* January 4, 1919.

FIG. 1.—Sub-bifurcation block: *B* and *C* are similar, yet a period of twenty-one months intervened. *A* illustrates the difficulty in localizing definitely the seat of the block. It is possible either that the block began in the finer ramifications of the bundle, later extending to the main branch, or that the block occurred in the larger branches from the onset.

which the patient's clinical condition became progressively worse, showed a progressive diminution in amplitude to two scale divisions. A final record taken during a period of improvement after operation showed a return to wider deflections (four scale divisions).

That conclusions based on progressive decrease of amplitude might result in error is exemplified by the following:

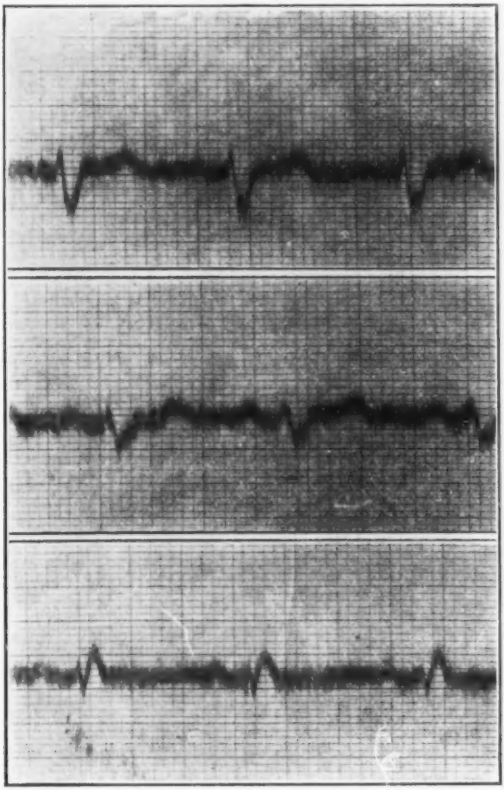
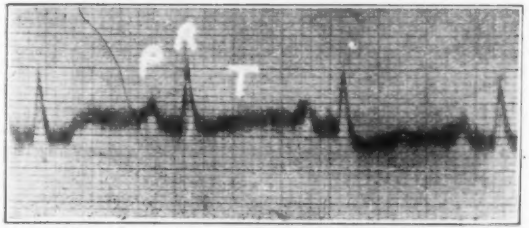


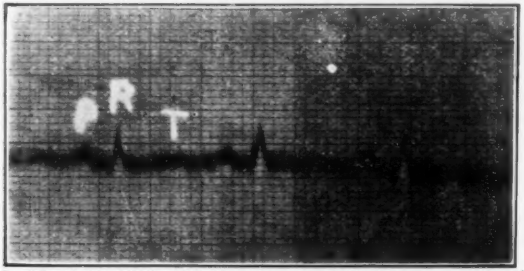
FIG. 2.—Sub-bifurcation block: Occurring in a patient without symptoms, suggesting cardiac disease. H. J. M., aged fifty-seven years. Referred by an oculist for headaches.

R. G., female, aged seventy-eight years. Admitted May 11, 1916. Clinical diagnosis: acute endocarditis superimposed upon chronic mitral and aortic valvular disease; chronic myocarditis; pulsus alternans. Clinical condition of patient became progressively worse while in the hospital. Electrocardiogram on admission showed normal height of deflections, ten scale divisions, Lead I. Patient

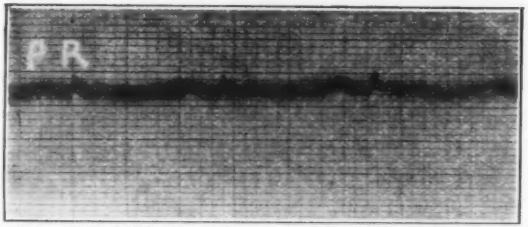
FIG. 1.—Sub-bifurcation block: *B* and *C* are similar, yet a period of twenty-one months intervened. A mistake in possible either that the block began in the finer ramifications of the bundle, later extending to the main branch, or that the block occurred in the larger branches from the onset.



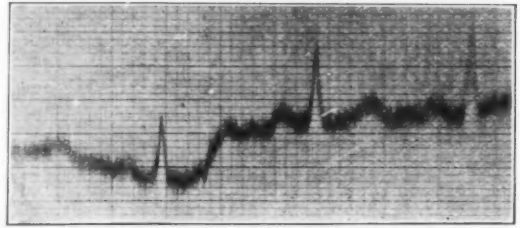
A. February 3, 1920. E. F. D., aged twenty-four years. Serofibrinous pericarditis of tubercular origin; effusion, later becoming purulent. Patient able to walk without dyspnea.



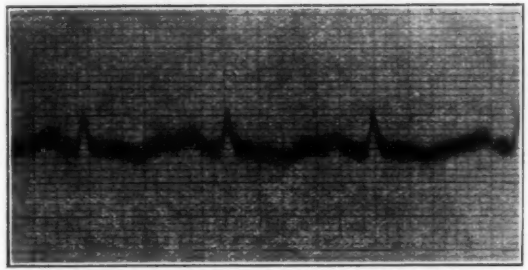
B. March 29, 1920. Effusion more marked. Decompensation severe.



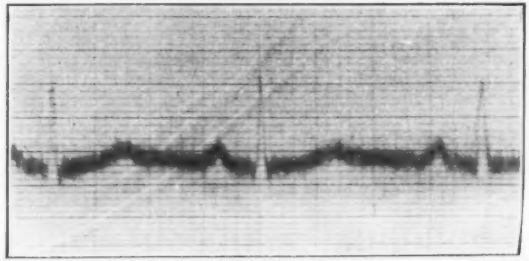
C. April 16, 1920. Forty hours after drainage of pus from peri-



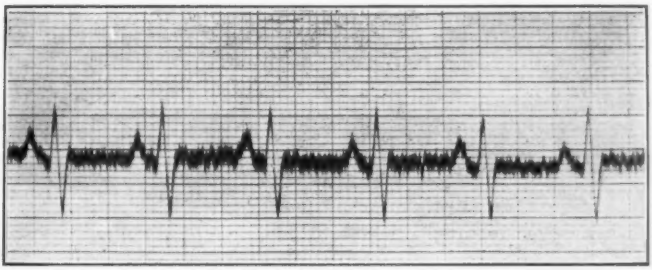
D. April 16, 1920. Control.



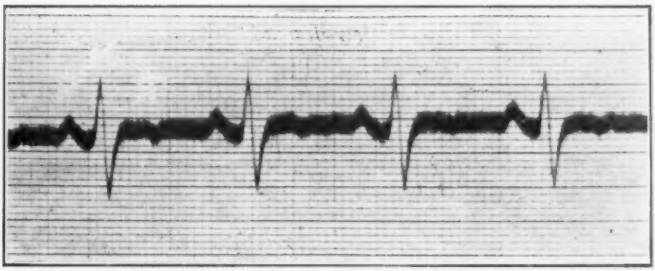
E. April 29, 1920. Increased amplitude thirteen days after operation. Subjective and objective improvement.



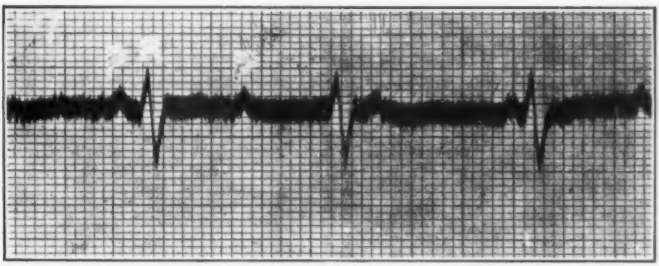
F. April 28, 1920. Control.



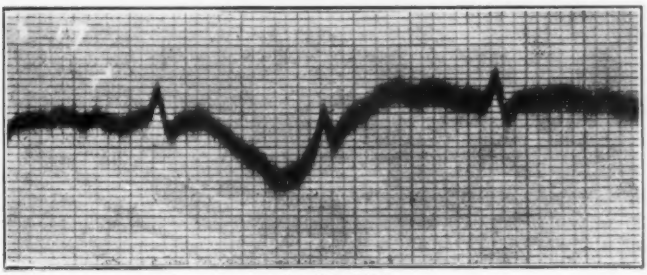
A. June 13, 1916.



B. February 3, 1917.

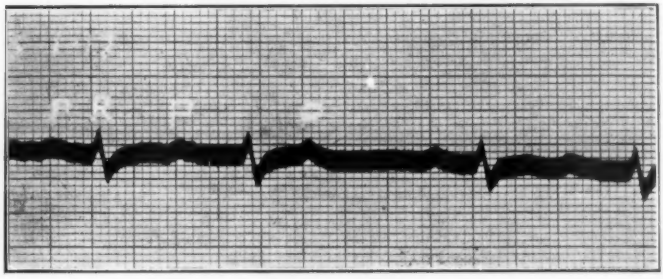


C. March 6, 1917.

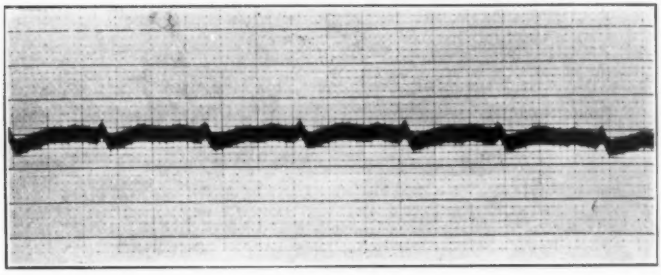


D. April 6, 1917.

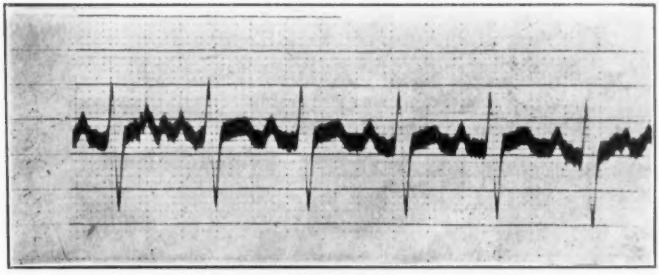
FIG. 4.



E. May 1, 1917.



F. May 15, 1917.

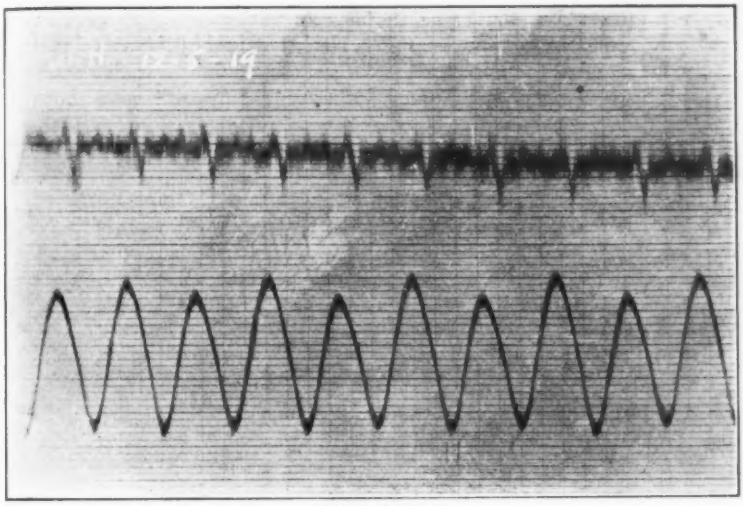


G. May 18, 1917.

FIG. 4a.—Decreased amplitude. Height varying with clinical condition during period of eleven months; sudden return to normal amplitude nineteen days before patient's death and at period when decompensation was profound. R. G., aged seventy-eight years. Acute endocarditis, superimposed upon chronic mitral and aortic valvular disease. Chronic myocarditis; pulsus alternans.

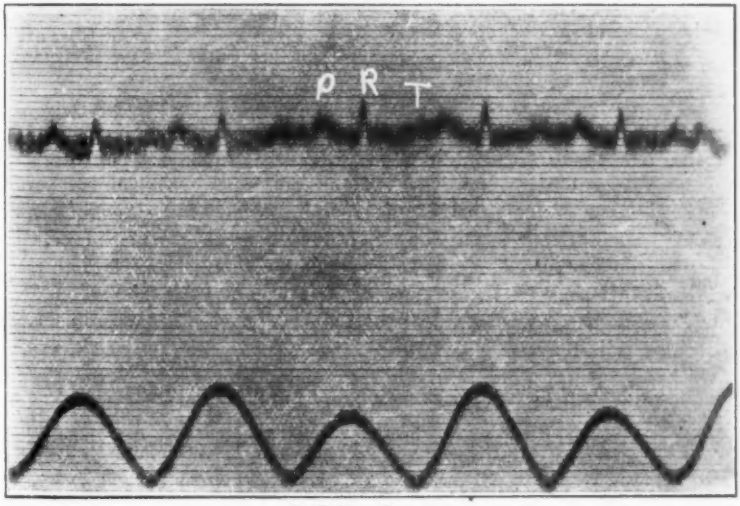
discharged November 2, 1916, no further electrocardiogram being taken. Readmitted January 4, 1917. Patient died June 6, 1917. Patient's clinical condition became progressively worse after second admission. The amplitude of the primary deflections became gradually smaller (from seven to one scale divisions). However,

there was one striking exception; a final electrocardiogram nineteen days before death showed that the deflections had returned to ten scale divisions.



A. Pulsus alternans.

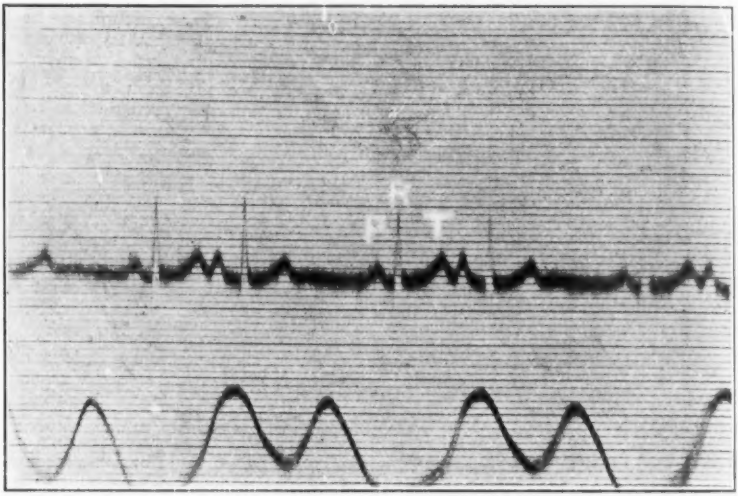
FIG. 5.



B. Pulsus alternans.

FIG. 5*a*.

III. Prolongation of the *P–R* interval over the normal of 0.2 second may be due to various causes such as acute infections, drug action and degenerative processes affecting heart muscle. There is considerable difference of opinion among observers as to the normal *P–R* interval. Lewis[8] states that "prolongation over 0.20 second is never found in healthy hearts." Hecht[9] regards 0.14 as normal; F. N. Wilson[10] accepts 0.17. Within certain limits each patient sets his own standard. Cohn, Jamieson and Frazer[11] have shown



C. Coupling due to premature beats; patient referred to heart station as case of supposed alternation.

FIG. 6.—Type of tracing obtained by apparatus illustrated in Fig. 7.

that digitalis can prolong the *P–R* interval. Hence unless digitalis influence can be excluded, no conclusions as to prognosis can be based upon prolongation of the *P–R* interval. Such deductions could not be made in patients of our series since regarding most of them no reliable history as to previous medication was available. On the other hand it is exactly in the type of patient in which a prolongation of *P–R* interval might be expected that digitalis is most liable to be administered.

[8] Vide supra, p. 37.

[9] Der Mechanismus der Herzaktion im Kindersalter, seine Physiologie und Pathologie, Ergeb. d. inn. Med. u. Kinderh., Berlin, 1913, ii, 324; quoted by Rupe: Mod. Med., March, 1920, ii, 215.

[10] Recent Progress in Pediatrics, Résumé on the Circulation, Am. Jour. Dis. Children, 1915, x, 376; quoted by Rupe: Loc. cit., p. 215.

[11] The Influence of Digitalis on the T-wave of the Human Electrocardiogram, Jour. Exper. Med., June, 1915, xxi, 593.

IV. Since such inversion is always or nearly always pathologic, according to Lewis[12] inversion of T_1 "is often associated with signs or symptoms of ill omen." This author published figures[13] in which an invert T_1, which followed temporary deformity of primary ventricular complex, became upright when that deformity disappeared. The first curve was taken during a febrile attack, the second, one day later, after the subsidence of fever. Willius[4] states that a close connection exists between inversion of T_1 and disease of myocardium. Cohn[11] and his associates have shown that digitalis can modify T in that a T which was upright in the initial curve may be lowered first and finally inverted. Inversion of T_1 has been noted by White[6] in connection with hypothyroidism the T "tending to become more positive" in the presence of clinical improvement during thyroid feeding. Morrison[14] has noted that changes in the electrocardiogram following bleeding, hot-packs, ingestion of water and fasting may in certain persons affect the form of the electrocardiogram. Harris[15] while admitting that digitalis may affect T_1, draws definite conclusions on inversion of T_1 as observed in 16 of 40 patients electrocardiographed in an out-patient clinic. The cases electrocardiographed were selected on account of dyspnea on exertion, fainting fits and edema. Apparently no history of previous medication was sought, since no mention of absence of digitalization is made in this author's text or accompanying table; yet Harris has the temerity to conclude that "an invert T in the Lead I is reliable evidence of a damaged heart muscle."

Fifty-three cases in our series show inversion of T_1. In 26 of these T_1 was inverted alone. In only 1 case was it possible definitely to rule out digitalis. Hence we are unable to draw any deductions as to the significance of invert T_1 as personally observed.

V. From the standpoint of prognosis, alternation of the pulse, as occurring in hearts beating at an approximately normal rate, is a finding of extreme gravity. Unfortunately the electrocardiograph is capable of recording only the alternation of heart-action currents. The fact that curves showing such a disturbance of mechanism are rare is confirmed by our series in which the finding was present regarding but 0.55 per cent. of all patients examined. It is unfortunate that the electrocardiograph is incapable of demonstrating the disturbance of mechanism underlying the alternating pulse, since the latter finding, if sought for as routine, is found to be of frequent occurrence. Obviously, the value of the string galvanometer would be enhanced if it were possible to record simultaneously

[12] Clinical Electrocardiography, London, Shaw, 1913, p. 28.
[13] Idem, p. 29.
[14] Changes in the Electrocardiogram due Possibly to Alterations in Blood Volume, Proc. Soc. Exper. Biol., and Med., 1916–1917, xix, 64.
[15] Significance of an Inverted "T" in the First Lead of the Cardiogram, Lancet, February, 1919, i, 168.

electrocardiograms and pulse-waves. Our discussion of alternation will be limited to the description of an apparatus which we have devised to fulfil this indication.

The device which we are using combines the simplicity of the cuff method of Herrick[16] with the accuracy of the electrocardiogram. It therefore obviates the various sources of error of the former while preserving much of its simplicity of application. Used by us first only when a sphygmograph was not available, it is now used as routine on all arteriosclerotic patients and on those exhibiting premature contractions. The apparatus which is both time-saving and inexpensive may be visualized by reference to the accompanying illustration (Fig. 7).

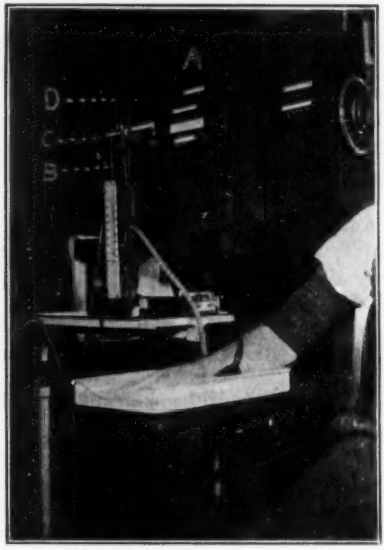


FIG. 7.—Recording apparatus for reading pulse waves in connection with simultaneous electrocardiogram; used for detection of pulsus alternans. *A*, camera; *B*, straw attached to cork float which rides on mercury; *C*, transverse arm of lever, which rests on straw; *D*, upright arm of right-angled lever, which oscillates in front of camera lens.

The oscillations of the mercury column of a sphygmomanometer are transferred to a right-angled lever, the upright arm of which moves in front of the slit of the camera of an electrocardiograph. The cuff of the sphygmomanometer is applied in the usual manner and the tracing is taken at a pressure slightly below that ordinarily accepted as the systolic pressure.

[16] Pulsus Alternans Detected by the Sphygmomanometer, Jour. Am. Med. Assn., February, 1915, lxiv, 739.

We claim no originality in the production of a combined electrocardiogram and pulse-tracing. Methods of producing such combined records abound. It is even quite possible that other investigators have employed the principle upon which our appliance is based. As we have seen no reference in the literature to such an application, however, we feel justified in describing it here. The accompanying figures are illustrative of the results obtained.

Conclusions. 1. Electrocardiographic curves are capable of furnishing important information as to the efficiency of the heart muscle.

2. As cardiac failure is due to myocardial insufficiency the electrocardiograph can furnish information valuable from the standpoint of prognosis.

3. Conduction defects below the bifurcation of the bundle of His may be associated with a characteristic electrocardiogram. It is often difficult to determine whether such defect is in the branch bundle or in the terminal arborization. The defect may be functional or it may be due to histologic change. In the latter case the prognosis is grave.

4. Decreased amplitude of the primary ventricular deflections is at times found to have a striking relationship to clinical evidence of a failing heart. Exceptions to this relationship occur, and, as there are several possible sources of error in obtaining reliable curves, observations should be carefully controlled and definite conclusions withheld until the subject is further elucidated.

5. Prolongation of P–R interval and inversion of T_1 have been associated by various observers with degenerative processes in heart muscle. A prolongation of P–R and an inversion of T_1 can also be brought about by digitalis action, and it is precisely in the class of cases in which information as to the P–R interval and inversion of T_1 could be of value that digitalis is liable to have been administered. Conclusions as to the condition of heart muscle as based on the presence of one or the other of these deformities must be confined to patients from whom digitalis effect can be excluded. Analysis of our series has shown that digitalis effect can seldom be excluded in such patients as are routinely referred to a heart station. Hence, prolongation of P–R and inversion of T_1 are liable to be of little prognostic significance in such patients.

6. A discussion of pulsus alternans does not come properly within the scope of this paper, since the underlying disturbance of mechanism can seldom be demonstrated by the string galvanometer. This fact is unfortunate, since the recognition of an alternating pulse carries with it so grave a prognosis that the search for this finding should be routine in certain classes of patients. A simple device is described whereby galvanometric curves and pulse waves can be simultaneously recorded. This can be done with but little expenditure of time, and the method has therefore become routine in our laboratory.

7. The practical value of laboratory evidence as to the presence of disease of the heart muscle is inversely proportionate to the skill of the attending physician in interpreting clinical evidence as to the imminence or presence of heart failure. Such skill is possessed chiefly by the internist. Yet internists furnished 61.5 per cent. of all cases examined. The statistics of other heart stations would probably be similar. It becomes, therefore, the duty of the internist to instruct members of other branches of the profession regarding the necessity of more frequent use of instruments of precision in the diagnosis and prognosis of disease of heart muscle.

NOTE.—The authors acknowledge their indebtedness to Dr. A. P. D'zmura for assistance in the preparation of this paper.

OBSERVATIONS ON NEGATIVITY OF THE FINAL VENTRICULAR T WAVE OF THE ELECTROCARDIOGRAM.*

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A REVIEW of the literature on electrocardiography, both experimental and clinical, at once reveals a variance in views as to the interpretation of the normal electrocardiogram. The two views that have gained broadest recognition are: (1) All waves are manifestations of excitation and contraction of heart muscle, and (2) the waves result from electric changes accompanying conduction of the impulse and contraction of the muscle.

Einthoven assumed that the right ventricle represents the cardiac base and the left ventricle the apex, and that the dominance of negativity in the right ventricle causes an upward deflection while dominance in the left causes a downward deflection of the galvanometer. Thus the *R* wave is ascribed to contraction of the right heart, the *S* wave to contraction of the left heart and the horizontal *S–T* interval to neutralization of basal and apical negativity. The *T* wave represents contraction of the right ventricular base outlasting that of the left.

Eppinger and Rothberger object to Einthoven's assumption in ascribing the rôle of cardiac base to the relatively weak right ventricle and regarding the left ventricle with its massive muscle bulk as the apex.

The views of Kraus and Nicolai are based on the structural arrangement of the ventricular musculature into systems. Follow-

* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the Degree of Master of Science in Medicine, May, 1920.

ing auricular contraction the impulse passes through the auriculoventricular bundle and its contiguous structures. The long *P–R* interval is explained by slow conduction and the absence of appreciable action currents at this time due to the small muscle mass. The *R* wave is ascribed to primary activity of the basal portions of the papillary muscles. As the excitation wave spreads toward the apex the termination of the *R* wave occurs. The *S–T* interval is explained by the absence of potential between base and apex. The *T* wave results from late return of negativity to the base.

The views of Einthoven, Kraus and Nicolai agree in general in emphasizing the antagonistic action of electric potential between base and apex.

In distinct opposition to the views already expressed, Hoffmann concluded that the electrocardiogram results from two actions, impulse conduction and muscle contraction. The *Q R S* complex results from passage of the impulse through the ventricular conduction system and the *S–T* interval and the *T* wave from electric potential caused by the contracting ventricle. Hoffmann produced standstill of the frog heart by the application of muscarin, obtained simultaneous electrocardiographic and ventricular suspension curves and found that the electrocardiogram of the nonbeating heart differs from the normal only in the absence of the *T* wave. When the muscarin effect was abolished by atropin and the beats returned the *T* wave reappeared.

Eyster and Meek, as a result of their experimental work on the relation of the line of isopotential to the formation of the electrocardiogram and their critical review of the literature, in general agree with Hoffmann's theory. They believe the *R* wave to be concerned with conduction, but they do not ascribe definite structures as conducting mediums. The *T* wave is the expression of preponderance of contraction on one side of the line of equipotential. Eyster and Meek further show the differences between physiologic curves of conduction and contraction. When a nerve is stimulated where conduction alone occurs a single monophasic or diphasic electric response occurs. In skeletal muscle this rapid electric change is followed by a slower and more prolonged electric variation. This conforms with the general contour of the electrocardiographic deflections; the *R* wave is abrupt and steep, the *T* wave blunt and prolonged.

Cardiac Events and the Electrocardiogram.

The relationship of the waves of the electrocardiogram to definitely known cardiac events strongly supports the "conduction contraction" theory. By a consideration of accepted relationships of the normal heart sounds a working basis for comparison is established.

Einthoven, Flohil and Battaerd have shown that the first sound begins at the initiation of ventricular systole and lasts from 0.07 to 0.10 second, is followed by a pause varying from 0.15 to 0.25 second and then succeeded by the second sound. These observations have been confirmed by other investigators.[1 10 35] The second sound follows closely on the closure of the semilunar valves,[37] begins simultaneously with the rise of intraventricular pressure[14] and gains its maximum amplitude during this period.[33] That the second sound is an early diastolic event has been shown clearly.[26 36]

Kahn has demonstrated that the first sound falls in the pause between the *R* and the *T* waves and begins at the moment the *R* wave disappears and a short time before the rise of the *T* wave. The second sound begins 0.05 second after the end of the *T* wave. This relationship reveals the fact that the *R* wave is completed before ventricular contraction begins and indicates conduction rather than contraction. The *T* wave definitely occupies the period associated with actual ventricular contraction.

In clinical studies of the abnormalities of the *Q R S* group they are largely ascribed to disease of the ventricular conduction system.[3 24 34 38 31] It must be recognized, however, that the graphic representation of contraction in the electrocardiogram is the expression of changes in electric potential and not the translation of actual contraction. The iso-electric portion of the intervals *S–T* and a portion of *T–P* are not latent in the sense of a refractory phase.

Consideration of Electropotential.

Waller and Reid demonstrated a line of equipotential passing through the heart from base to apex in relation to any two derivations from the extremities. A preponderance of negativity above this line, representing the cardiac base, caused deflection of the galvanometer connected to both upper extremities in a manner to indicate relative negativity of the electrode connected with the right arm. The arm becomes relatively negative in derivations from an arm and a leg. Dominance of negativity below the equipotential line deflects the galvanometer in the opposite direction.

Hypothesis of *T*-wave negativity.

The three derivations of the electrocardiogram possess symbols of definite electropotential in relation to their electrodes. In the normal electrocardiogram derivation 1 bears symbols as follows: right arm −, left arm +; derivation 2, right arm −, left leg +; and derivation 3, left arm −, left leg + (Fig. 1). This arragement implies positive or upright deflections in all derivations of the electrocardiogram. If it is assumed that the "conduction-con-

traction" theory is correct the *T* wave is the expression of preponderance of contraction on one side of the line of equipotential. *T*-wave negativity (inverted) therefore results from changes in contraction preponderance. The negativity of this wave in certain isolated or combined derivations of the electrocardiogram is indicative of definite potential changes affecting contraction preponderance in various regions of the cardiac musculature.

In the normal heart, therefore, according to standard derivations, the *T* wave in all derivations is positive (upright), the upper right zone of potential is strongly electronegative to the apical zone while the left upper zone is iso-electric. This potential arrangement is illustrated in Fig. 1.

For reasons of simplification I have represented the three derivations by the sides of an equilateral triangle. To prevent misunderstanding it should be stated that the schematic figure employed, divided into zones of electropotential, is not based on mathematic consideration. The right upper zone in general corresponds to the sinus region of the heart and in the normal potential arrangement is electronegative.

Confirmation of this is found in the researches of Keith and Flack, Wybauw, Lewis, Oppenheimer and Oppenheimer, Brandenburg and Hoffmann, and Ganter and Zahn, who have shown that the cardiac impulse takes its origin in a collection of specialized tissue, a remnant of the primordial sinus. This structure lies in the sulcus terminalis at the juncture of the superior vena cava and the right auricular appendage, and is the seat of primary cardiac negativity.

Changes in the normal potential distribution produce *T* wave negativity in isolated or combined derivations of the electrocardiogram. Reversal of potential in one derivation alters cardiac potential so that *T*-wave negativity in that derivation occurs.

T-WAVE NEGATIVITY.

Many opinions have been expressed as to the significance of negativity or inversion of the *T* wave in isolated or combined derivations of the electrocardiogram.

The effect of digitalis on the heart as manifested by negativity of the *T* wave is well known;[4] it has been ascribed to muscular ventricular redistribution or possibly to alteration in muscular contractility. These changes are not permanent.

Numerous statements may be found in which myocardial damage is ascribed to *T*-wave negativity in certain derivations,[3 18 19 25] and again these occurrences have been noted in apparently normal hearts[13 20 31] affecting largely derivation 3.

Smith during his experimental work on coronary ligations observed interesting changes in the *T* wave. The most constant

Positive T wave in all Derivations (normal)

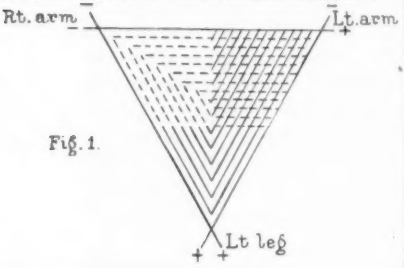

Fig. 1.

Negative T wave in Derivation I.

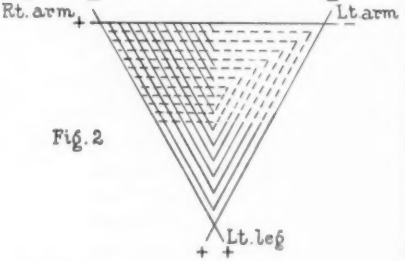

Fig. 2

Negative T wave in Derivation III.

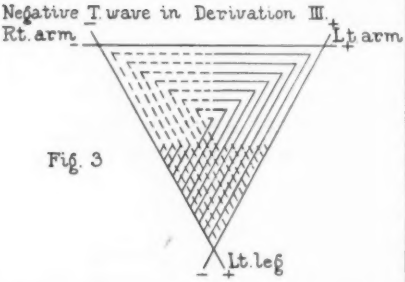

Fig. 3

Negative T wave in Derivations I and II.

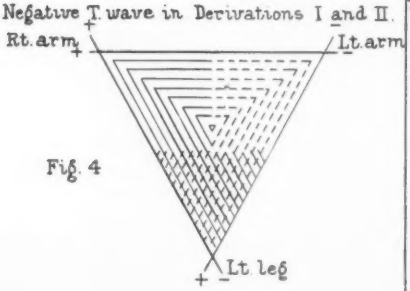

Fig. 4

Negative T wave in Derivations II and III

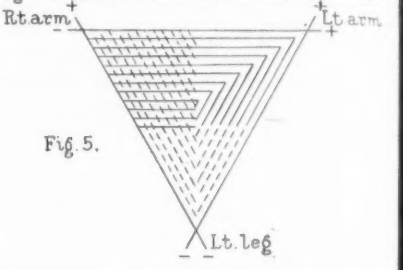

Fig. 5.

Negative T wave in Derivations I, II and

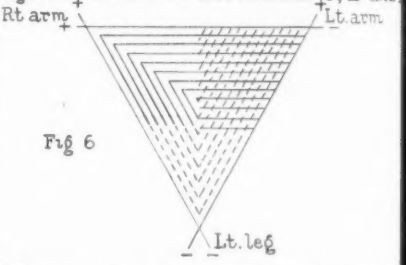

Fig 6

Diffuse iso-electric state of heart if negat
T. wave in Derivation II occurred.

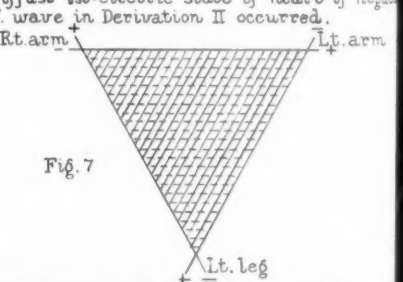

Fig. 7

Diffuse iso-electric state of heart if negati
T. wave in Derivations I and III occurred

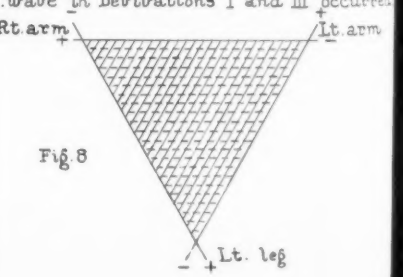

Fig. 8

Observations on negativity of the final ventricular *T* wave of the electrocardiogram.

changes in the electrocardiogram following ligation of any branch of the left coronary artery affected the *T* wave. A strongly positive to a markedly negative wave resulted fairly constantly with a slower return to positive or iso-electric. The negativity was usually observed within twenty-four hours after ligation and lasted for from three to four days. The duration seemed to bear a relationship to the size of the artery ligated. This work offers a tangible basis in directing attention to changes in the intrinsic blood supply of the heart, as evidenced by greater or lesser derangements of cardiac function. Morison has shown that blood-volume alterations may produce changes detectable in the electrocardiogram.

Increased general cellular function implies increased blood volume for the maintenance of normal tissue metabolism. In a specialized organ this augmentation is manifested by an increase in its function. In the heart increase in the blood volume beyond physiologic limits increases contraction. I refer particularly to increase of ventricular blood volume, since coronary volume is largely dependent on this factor. Because of impairment or disease of certain intrinsic channels of blood supply the affected muscle does not receive the requisite amount of blood properly to maintain function while the unaffected muscle demands greater blood volume for relatively more efficient contraction. This is an explanation for *T*-wave changes in isolated or combined derivations occurring permanently or temporarily.

The Action of the Cardiac Nerves on *T*-wave Negativity.

Stimulation of the cardiac vagus has been shown to produce negativity of the *T* wave,[5 29] and the same observation is noted following stimulation of the left cervical sympathetic branches.[28]

A series of clinical observations were conducted on patients having negative *T* waves in isolated or combined derivations of their electrocardiograms. Following the initial tracing, pressure was applied in turn to the right vagus region in the neck, to the left vagus region and finally to the right eyeball (oculocardiac reflex) and the respective electrocardiograms obtained. In no instance was any change noted in the negative *T* wave or in the positive *T* wave of the unaffected derivations. Atropin (gr. $\frac{1}{150}$) was then administered subcutaneously and records obtained every ten minutes for forty minutes. Again no effect on the *T* wave was noted. No change occurred following the subcutaneous administration of adrenalin (0.5 c.c. of a 1 to 1000 solution). These clinical procedures, however, are obviously not so accurate as direct experimental stimulation.

The present status of cardiac histopathology fails to explain many derangements of function. Histologic studies do not indicate why auricular fibrillation occurs in one heart and auricular

flutter in another. Disease of the cardiac conduction system is more definite histologically. Involvement below the auriculoventricular bundle is often associated with unquestionable intrinsic vascular changes.

There has been no adequate explanation of the occurrence of the negative *T* wave in isolated or combined derivations of the electrocardiogram. In the Mayo Clinic we have repeatedly observed the negative *T* wave in derivation 1, in derivation 3, in combined derivations 1 and 2, in combined derivations 2 and 3 and in combined derivations 1, 2 and 3. No instances of negativity in derivation 2 or in combined derivations 1 and 3 are recorded. This observation in 7000 electrocardiographic examinations eliminates the element of coincidence. There is a definite reason why these changes do not occur. Lewis states that the *T* wave is always upright in derivation 2 alone.

T-wave Negativity in Derivation 1 (Fig. 2). Fig. 2 represents the arrangement of potential existing with this abnormality. The left arm becomes electronegative to the right while the other signs remain unchanged. The right upper zone instead of being electronegative becomes iso-electric while the left upper becomes electronegative to the apex. The occurrence of an iso-electric state in the right upper zone is a marked departure from the normal in that the area of primary electronegativity is altered.

T-wave Negativity in Derivation 3 (Fig. 3). The left leg becomes electronegative to the left arm; the other derivations remain unchanged. The right upper zone remains electronegative with reference to the left upper. The apical zone becomes iso-electric. This distribution is but a slight deviation from normal in that the right upper zone remains electronegative.

T-wave Negativity in Combined Derivations 1 and 2 (Fig. 4). The left arm becomes electronegative to the right arm and the left leg electronegative to the right arm. The third derivation remains unchanged. The left upper zone becomes electronegative to the right and the apical zone becomes iso-electric. This arrangement again deviates from the normal in altering the area of primary electronegativity; it is a lesser change in that the right upper zone becomes electropositive instead of iso-electric.

T-wave Negativity in Combined Derivations 2 and 3 (Fig. 5). The left leg becomes electronegative to both arms. Derivation 1 remains unchanged. The apical zone becomes electronegative to the left upper while the right upper zone becomes iso-electric. This arrangement as in Derivation 1 is a marked change from normal in that the area of primary electronegativity becomes iso-electric.

T-wave Negativity in Combined Derivations 1, 2 and 3 (Fig. 6). All derivations reverse their signs in relation to each other. The apical zone becomes electronegative to the right upper while the left upper zone becomes iso-electric. The upper zones assume

just the opposite relationship to each other that occurs in combined derivations 2 and 3. Here again the potential distribution is disturbed, the area of primary electronegativity becoming electropositive, approaching the changes accompanying *T*-wave negativity in combined derivations 1 and 2.

Figs. 7 and 8 illustrate the reason why *T*-wave negativity in derivation 2 and in combined derivations 1 and 3 does not occur. In derivation 2 the left leg would be electronegative to the right arm while the other derivations would remain unchanged. This distribution would imply a diffuse iso-electric cardiac state and would indicate that cardiac contraction had ceased. In combined derivations 1 and 3 the left arm would be electronegative to the right and the left leg to the left arm. This arrangement likewise would indicate a diffuse iso-electric state.

The greater the deviation from the normal potential distribution the greater the significance of the disorder responsible for the change. The greatest change occurring which is compatible with life is the iso-electric state occupying the right upper zone. Therefore *T*-wave negativity in derivation 1 and in combined derivations 2 and 3 should be associated generally with grave heart disease. Next in significance should be those distributions of potential rendering the left upper zone electronegative to the right and represented by *T*-wave negativity in combined derivations 1 and 2 and in combined derivations 1, 2 and 3.

In the distribution which most closely approximates normal the *T* wave is negative in derivation 3. In these cases the normal potential relationship of the right upper zone is maintained.

Clinical Consideration of *T*-wave Negativity.

This study comprises 1106 cases of *T*-wave negativity in the electrocardiograms. One hundred and forty instances (12.6 per cent.) were noted in derivation 1, 688 (62.2 per cent.) in derivation 3, 62 (5.6 per cent.) in combined derivations 1 and 2, 171 (15.5 per cent.) in combined derivations 2 and 3, and 45 (4.1 per cent.) in combined derivations 1, 2 and 3. There was no instance of *T*-wave negativity in derivation 2 nor in combined derivations 1 and 3. Patients who had had digitalis within six weeks of the time of electrocardiographic examination were not included in this series.

T-wave Negativity and Ventricular Preponderance.

In the complete series about half (46.6 per cent.) of the electrocardiograms were associated with preponderance of the left ventricle. Preponderance of the right ventricle is evidenced by a negative *R* wave in derivation 1 and by a positive *R* wave in deri-

vation 3. In cases of preponderance of the left ventricle these changes are reversed. Right preponderance was infrequent (17.3 per cent.) and no unbalance was present in 36.1 per cent. of the electrocardiograms. Preponderance of the left ventricle occurred most often associated with *T*-wave negativity in derivation 1 and in combined derivations 1 and 2. No instance of right preponderance was noted with negativity in combined derivations 1, 2 and 3. These observations are summarized in Table I.

TABLE I.—T-WAVE NEGATIVITY AND VENTRICULAR PREPONDERANCE.

Derivation.	Total.	Left preponderance.	Percentage.	Right preponderance.	Percentage.	None.	Percentage.
1	140	120	85.7	5	3.6	15	10.7
3	688	274	39.8	132	19.2	282	41.0
1 and 2	62	52	83.9	4	6.4	6	9.7
2 and 3	171	43	25.2	51	29.8	77	45.0
1, 2 and 3	45	27	60.0	0	0	18	40.0
Total	1106	516	46.6	192	17.3	398	36.1

TABLE II.—GRAVE HEART DISEASE ASSOCIATED WITH T-WAVE NEGATIVITY.

Derivation.	Total.	Arborization block.	Delayed auriculoventricular conduction.	Complete auriculoventricular dissociation.	Auricular fibrillation.	Auricular flutter.	Ventricular tachycardia.	Aortic disease.	Angina pectoris.
1	140	53	3	3	19	1	1	16	9
3	688	13	2	0	11	0	0	8	21
1 and 2	62	14	2	0	5	0	1	6	1
2 and 3	171	11	3	1	24	0	1	13	3
1, 2 and 3	45	3	3	0	11	0	0	8	2
Total	1106	84	13	4	70	1	3	51	36

Associated Diseases.

T-wave Negativity in Derivation 1 (140 cases). Myocardial degeneration associated with the hypertension group occurred with greatest frequency (38.6 per cent.) in the patients having *T*-wave

negativity in derivation 1 of their electrocardiograms. Three factors are probably responsible for the myocardial changes accompanying hypertension: (1) The cause or causes primarily responsible for the constitutional disorder; (2) the action on the myocardium of the retention products or of the intermediate products of incomplete metabolism or toxic agents resulting from imperfect renal or tissue function; and (3) the increased cardiac work, affecting largely the myocardium, resulting from the hypertension *per se* and the alterations in cardiovascular balance.

Chronic endocarditis occurred second in order of frequency (22.1 per cent. of the cases). The myocardial damage attending this disorder occurs concomitant with or secondary to the endocardial invasion (Table III). In no instance was the cardiac examination negative. In the majority of instances grave heart disease was present.

TABLE III.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATION 1.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
11 to 20	2	0	0	0	2	0	0	0	0	0	0	0
21 to 30	5	0	0	0	4	1	0	0	0	0	0	0
31 to 40	7	1	0	0	3	2	0	0	0	0	0	1
41 to 50	28	10	2	2	7	1	5	1	1	0	0	0
51 to 60	40	16	1	2	6	6	2	7	4	0	0	0
61 to 70	54	25	0	2	9	7	0	11	4	0	0	0
71 to 80	4	2	0	0	0	2	0	0	0	0	0	0
Total	140	54	3	6	31	19	7	19	9	0	0	1
Per cent	...	45			40.7			13.6		...	...	0.7

Fifty-three patients had arborization block, 3 had delayed auriculoventricular conduction, 3 had complete auriculoventricular dissociation, 19 had auricular fibrillation, 1 had auricular flutter and 1 had ventricular tachycardia. Sixteen patients had aortic disease. Nine had angina pectoris.

The high incidence of grave heart disease in this group verifies my previous statement regarding the potential distribution responsible for this negativity as being the greatest departure from normal. The right upper zone is iso-electric instead of electronegative.

T-wave Negativity in Derivation 3 (688 Cases). The relative frequency of *T*-wave negativity occurring in derivation 3 is at once apparent.

The myocardial degeneration secondary to exophthalmic goiter was the most frequently associated condition (19.2 per cent.). Myocardial damage due to exophthalmic goiter involves the cellular action of thyroxin[17] (thyroid active principle) on the myocardium[27] and the increased cardiac work accompanying the rise of the basal metabolic rate.

Chronic endocarditis occurred in 16.9 per cent. and chronic myocarditis in 14.8 per cent. By chronic myocarditis I refer to those cases of inflammatory origin in contradistinction to the cases of myocardial degeneration. Myocardial degeneration associated with the hypertension group occurred in only 10.8 per cent. of cases (Table IV).

TABLE IV.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATION 3.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
1 to 10	10	0	0	0	4	0	0	0	0	4	0	2
11 to 20	62	2	20	0	13	2	1	0	0	0	22	2
21 to 30	190	6	55	3	40	19	2	0	0	1	46	18
31 to 40	161	12	39	5	32	15	6	0	0	0	35	17
41 to 50	138	28	16	5	18	25	5	4	4	1	19	17
51 to 60	83	21	2	9	5	27	5	7	6	0	1	6
61 to 70	39	4	0	2	4	12	0	12	10	0	2	3
71 to 80	5	1	0	0	0	2	0	2	1	0	0	0
Total	688	74	132	24	116	102	19	25	21	6	125	65
Per cent.	...	33.4			34.4			3.7		0.9	18.2	9.4

Grave heart disease is relatively infrequent in this group; 3 patients had arborization block, 2 had delayed auriculoventricular conduction and 11 auricular fibrillation. Eight patients had aortic disease and 21 had angina pectoris. Twenty per cent. of the patients had no demonstrable evidence of organic heart disease. Of this number 40 per cent. had cardiac neurosis.

The relative infrequency of grave heart disease and the high

percentage of apparently normal hearts in this group are in marked contrast to the findings associated with *T*-wave negativity in derivation 1. These findings are in accord with the hypothetic significance of *T*-wave negativity in derivation 3. The potential distribution in this *T*-wave negativity is illustrated in Fig. 3. The right upper zone remains electronegative, the other zones reverse their potential, establishing an arrangement which does not materially depart from the normal.

The potential distribution occurring in such a relatively high percentage of apparently normal hearts and the frequent transient *T*-wave negativity in derivation 3 make functional myocardial fatigue a causative possibility in a certain number of cases at least.

T-wave Negativity in Combined Derivations 1 and 2 (62 Cases). Myocardial degeneration associated with the hypertension group occurred in half (50 per cent.) of the patients having *T*-wave negativity in combined derivations 1 and 2. Chronic endocarditis was present in 20.9 per cent. of the cases. In no instance was the cardiac examination negative. These findings are summarized in Table V. About half (46.7 per cent.) of the cases were associated with grave heart disease. Fourteen patients had arborization block, 2 had delayed auriculoventricular conduction, 5 had auricular fibrillation and 1 had ventricular tachycardia. Six patients had aortic disease and 1 of these had an aortic aneurysm. One patient had angina pectoris.

TABLE V.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATIONS 1 AND 2.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
21 to 30	7	0	0	0	6	1	0	0	0	0	0	0
31 to 40	5	3	0	0	2	0	0	0	0	0	0	0
41 to 50	13	7	0	1	1	3	0	0	0	0	0	1
51 to 60	20	14	1	0	2	1	1	1	1	0	0	0
61 to 70	15	7	0	1	2	1	1	3	0	0	0	0
71 to 80	2	0	0	0	0	1	0	1	0	0	0	0
Total	62	31	1	2	13	7	2	5	1	0	0	1
Per cent.	...	54.8			35.5			8.1		...	...	1.6

Reference to the potential distribution responsible for *T*-wave negativity in this derivation combination (Fig. 4) shows that the normal potential (electronegativity) of the right upper zone is disturbed. The left upper zone becomes electronegative to the right upper. Although this is a distinct departure from normal it is less marked than those states in which the right upper zone becomes iso-electric.

T-wave Negativity in Combined Derivations 2 and 3 (171 Cases). Chronic endocarditis occurred with greatest frequency (26.9 per cent.) in those patients having *T*-wave negativity in combined derivations 2 and 3. In order of frequency followed myocardial degeneration associated with exophthalmic goiter (21 per cent.), chronic myocarditis (17.5 per cent.), and myocardial degeneration associated with the hypertension group (15.8 per cent.).

A large percentage of the patients had grave heart disease. Eleven patients had arborization block, 3 had delayed auriculoventricular conduction, 1 had complete auriculoventricular dissociation, 24 had auricular fibrillation and 1 ventricular tachycardia. Thirteen patients had aortic disease and 3 had angina pectoris. In 9 cases the cardiac examination was negative. These observations are illustrated in Table VI.

TABLE VI.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATIONS 2 AND 3.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
11 to 20	12	1	4	0	5	2	0	0	0	0	0	0
21 to 30	45	1	13	0	16	6	1	0	0	0	5	2
31 to 40	39	4	10	1	14	4	0	0	0	1	3	3
41 to 50	34	5	8	3	6	8	1	0	0	2	1	0
51 to 60	28	10	0	1	4	8	0	4	2	0	0	1
61 to 70	12	5	1	0	1	2	1	2	1	0	0	0
71 to 80	1	1	0	0	0	0	0	0	0	0	0	0
Total	171	27	36	5	46	30	3	6	3	3	9	6
Per cent.	...	39.8			46.2			3.5		1.7	5.3	3.5

Again the reader is referred to Fig. 5, which illustrates the potential distribution in *T*-wave negativity in this derivation combination. The similarity to the potential arrangement attending *T*-wave negativity in derivation 1 may be noted.

T-wave Negativity in Combined Derivations 1, 2 and 3 (45 Cases). *T*-wave negativity in derivations 1, 2 and 3 constituted the smallest group, comprising only 4.1 per cent. of the total series.

Myocardial degeneration associated with the hypertension group occurred most often (35.5 per cent.), and in order of occurrence chronic endocarditis (24.4 per cent.) and chronic myocarditis (20 per cent.). Every patient in this group had definite clinical evidence of heart disease (Table VII).

TABLE VII.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATIONS 1, 2 AND 3.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
11 to 20	1	0	0	0	1	0	0	0	0	0	0	0
21 to 30	4	0	0	0	2	1	0	0	0	1	0	0
31 to 40	7	1	0	0	4	1	1	0	0	0	0	0
41 to 50	9	2	1	2	0	3	1	0	0	0	0	0
51 to 60	12	8	0	0	2	0	0	2	1	0	0	0
61 to 70	12	5	0	0	2	4	0	1	1	0	0	0
Total	45	16	1	2	11	9	2	3	2	1	0	0
Per cent.	...	42.2			48.8			6.6		2.2		

Three of the patients with the graver forms of heart disease had arborization block, 3 delayed auriculoventricular conduction and 11 auricular fibrillation. Eight patients had aortic disease and 2 had angina pectoris. If the potential distribution in this disorder is taken into consideration the apical zone will be found electronegative to the right upper while the left upper zone will be iso-electric (Fig. 6). This arrangement is similar to that attending *T*-wave negativity in combined derivations 1 and 2 in that the right upper zone is electropositive. It likewise is a distinct deviation from normal.

TABLE VIII.—ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH T-WAVE NEGATIVITY.

Derivation.	Total.	T-wave negativity unattended.	Sinus arrhythmia.	Auricular premature contractions.	Auricular and nodal premature contractions.	Auricular and ventricular premature contractions.	Nodal premature contractions.	Nodal premature contractions and sinus arrhythmia.	Ventricular premature contractions.	Ventricular and nodal premature contractions.	Ventricular premature contractions and sinus arrhythmia.	Auricular fibrillation.	Auricular fibrillation and ventricular premature contractions.	Auricular fibrillation and aberrant Q R S complexes in isolated derivations.	Auricular fibrillation and aberrant Q R S complexes in isolated derivations and ventricular premature contractions.	Auriculoventricular block.	Auriculoventricular block and auricular premature contractions.	Auriculoventricular block and ventricular premature contractions.	Auriculoventricular block and auricular fibrillation.	Auriculoventricular block and delayed auriculoventricular conduction.	Aberrant Q R S complexes in isolated derivations.	Aberrant Q R S complexes in isolated derivations and auricular premature contractions.	Aberrant Q R S complexes in isolated derivations and ventricular premature contractions.	Delayed auriculoventricular conduction.	Delayed auriculoventricular conduction and sinus arrhythmia.	Delayed auriculoventricular conduction, aberrant Q R S complexes in isolated derivations and ventricular premature contractions.	Complete auriculoventricular dissociation.	Auricular flutter.	Nodal tachycardia.	Ventricular tachycardia.
1	140	41	0	2	0	6	0	0	0	11	0	0	8	6	1	0	36	3	8	4	2	2	1	2	1	0	0	0	3	1	1
3	688	550	24	14	1	8	4	1	0	40	0	1	17	4	0	1	10	0	2	0	0	10	0	1	0	0	0	0	0	0	0
1 and 2	62	32	0	2	0	2	1	0	2	1	0	3	1	0	0	0	11	0	1	0	1	2	0	0	1	0	0	0	0	0	1
2 and 3	171	112	1	5	0	1	1	0	10	1	0	20	4	0	0	0	4	0	5	1	1	1	0	0	1	1	0	1	0	0	1
1, 2 and 3	45	21	0	2	0	0	0	0	4	0	0	8	3	0	0	0	2	0	1	0	0	1	0	0	2	0	1	0	0	0	0
Total	1106	756	25	25	1	17	6	1	67	2	1	56	18	1	1	1	63	3	17	6	4	16	1	3	5	1	1	4	1	1	3

TABLE IX.—VALVULAR DISEASE ASSOCIATED WITH T-WAVE NEGATIVITY.

Decade.	Total.	Mitral disease.						Aortic disease.						
		Mitral regurgitation.	Mitral stenosis.	Double mitral lesion.	Mitral and polyvalvular regurgitation.	Double mitral lesion and aortic regurgitation.	Mitral stenosis and aortic regurgitation.	Aortic regurgitation.	Aortic stenosis.	Double aortic lesion.	Aortitis.	Aortic regurgitation and aortitis.	Aortic and polyvalvular regurgitation.	Aortic and mitral regurgitation.
1	37	16	0	2	1	2	0	3	2	2[1]	2[2]	5[3]	2[1]	0
3	122	64	27	7	0	2	0	10[3]	1	2	1[1]	2[2]	0	6
1 and 2	14	5	0	1	1	1	1	2	1	2[1]	0	0	0	0
2 and 3	49	22	7	5	2	0	0	4[1]	1	3	2[1]	1[1]	2	0
1, 2 and 3	12	4	0	0	0	0	0	3	0	2	0	3[1]	0	0
Total	234	111	34	15	4	5	1	22	5	11	5	11	4	6

[1] One patient in this group had syphilitic lesions.
[2] Two patients in this group had syphilitic lesions.
[3] Three patients in this group had syphilitic lesions.

Cardiac Mortality and *T*-wave Negativity.

T-wave Negativity in Derivation 1. Information has been received concerning 117 patients having *T*-wave negativity in derivation 1 of their electrocardiograms. Seventy-eight (66.6 per cent.) have died from heart disease during a period of four and a half years (Table X). The mortality in every decade is high; the lowest

TABLE X.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN DERIVATION 1.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
11 to 20	2	2	2	0	1	50.0	1	0	1	0	0
21 to 30	5	5	3	2	3	60.0	2	0	0	2	0
31 to 40	7	6	6	0	4	66.6	2	1	1	0	0
41 to 50	28	24	13	11	11	45.8	11	2	6	3	0
51 to 60	40	32	22	10	21	65.6	9	2	5	2	0
61 to 70	54	44	33	11	35	79.5	8	5	2	1	0
71 to 80	4	4	4	0	3	75.0	0	0	0	0	0
Total	140	117	83	34	78	66.6	33	10	15	8	0

percentage (45.8) occurred between the ages of forty-one and fifty. Thirty-three patients are alive and 10 of these report their conditions worse, 15 are improved and 8 are unchanged. None of the patients was without cardiac complaints.

The high cardiac mortality in this group is in accord with the hypothetic and clinical significance, previously emphasized, which attends this *T*-wave negativity. To prevent misunderstanding it may be stated that the negative *T* wave *per se* is only the manifestation of serious underlying myocardial disorder. Changes in cardiac function affecting contraction preponderance resulting from organic or functional myocardial fatigue alter electropotential, which produces *T*-wave negativity.

T-wave Negativity in Derivation 3. Information has been received concerning 487 patients having *T*-wave negativity in derivation 3 of their electrocardiograms. Forty-six (9.4 per cent.) have died from heart disease during a period of four and a half years. The data are summarized in Table XI. This relatively low cardiac

TABLE XI.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN DERIVATION 3.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
1 to 10 . . .	10	8	3	5	2	25.0	5	0	3	2	3
11 to 20 . . .	62	42	9	33	2	4.7	40	7	20	13	17
21 to 30 . . .	190	139	22	117	5	3.5	127	30	53	44	37
31 to 40 . . .	161	113	27	86	9	7.9	99	23	33	43	25
41 to 50 . . .	138	89	24	65	9	10.1	78	18	30	30	20
51 to 60 . . .	83	68	37	31	13	19.1	53	13	18	22	3
61 to 70 . . .	39	24	15	9	5	20.8	16	6	3	7	1
71 to 80 . . .	5	4	3	1	1	25.0	2	0	1	1	0
Total . . .	688	487	140	347	46	9.4	420	97	161	162	106

TABLE XII.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN COMBINED DERIVATIONS 1 AND 2

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
21 to 30 . . .	7	5	5	0	4	80.0	1	0	0	1	0
31 to 40 . . .	5	3	3	0	3	100.0	0	0	0	0	0
41 to 50 . . .	13	11	9	2	7	63.6	3	0	2	1	1
51 to 60 . . .	20	19	13	6	12	63.1	7	1	5	1	0
61 to 70 . . .	15	12	8	4	7	58.3	5	0	5	0	0
71 to 80 . . .	2	2	1	1	2	100.0	0	0	0	0	0
Total . . .	62	52	39	13	35	67.3	16	1	12	3	1

mortality is sharply contrasted with the mortality of the foregoing group. It is in agreement, however, with the hypothetic and clinical significance accorded *T*-wave negativity in derivation 3.

The potential distribution producing this negativity is but a slight departure from normal. Four hundred and twenty patients are alive, 97 report their conditions worse, 161 are improved and 162 are unchanged. One hundred six patients report no cardiac complaints.

T-wave Negativity in Combined Derivations 1 and 2. Of the 52 patients having *T*-wave negativity in combined derivations 1 and 2 concerning whom we have heard, 35 (67.3 per cent.) have died from heart disease during four and a half years. This mortality is greater than was anticipated in that the potential distribution resulting in this *T*-wave negativity was not the greatest departure from normal. In Fig. 4, in which the potential distribution is represented, the right upper zone becomes electropositive to the left instead of electronegative as in the normal, but this is a lesser departure than iso-electric. The fact that the group is relatively small may be a factor in obtaining a high cardiac mortality. Sixteen patients are alive, 1 reports his condition worse, 12 are improved and 3 are unchanged. Only 1 patient reports no cardiac complaint.

T-wave Negativity in Combined Derivations 2 and 3. We have learned of the condition of 135 patients having *T*-wave negativity in combined derivations 2 and 3. Thirty-five (25.9 per cent.) have died from heart disease during a period of four and a half years (Table XIII). In contradistinction to the foregoing group the mortality was lower than expected from a hypothetic consideration of potential distribution and associated heart disease. A possible explanation for this discrepancy rests in the fact that 23.3 per cent. of the patients were examined during the last year of the series, and the time element, therefore, is too short to embrace a true mortality average. Eighty-eight patients are alive, 25 report their conditions worse, 37 are improved and 26 are unchanged. Sixteen patients report no cardiac complaints; 7 of these had had thyroidectomies for hyperthyroidism and were cured.

TABLE XIII.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN COMBINED DERIVATIONS 2 AND 3.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
11 to 20 . . .	12	9	0	9	0	0	9	2	4	3	2
21 to 30 . . .	45	34	11	23	9	26.4	22	7	10	5	6
31 to 40 . . .	39	32	9	23	5	15.6	24	7	9	8	7
41 to 50 . . .	34	27	16	11	8	29.6	17	4	7	6	1
51 to 60 . . .	28	20	15	5	6	30.0	12	2	7	3	0
61 to 70 . . .	12	12	9	3	6	50.0	4	3	0	1	0
71 to 80 . . .	1	1	1	0	1	100.0	0	0	0	0	0
Total . . .	171	135	61	74	35	25.9	88	25	37	26	16

T-wave Negativity in Combined Derivations 1, 2 and 3. Patients having *T*-wave negativity in all derivations comprised a relatively small group. Nineteen of the 38 (50 per cent.) on whom we have had reports have died from heart disease during four and a half years (Table XIV). This mortality agrees fairly well with hypothetic considerations of potential distribution and associated grave heart disease (Fig. 6). Fifteen patients are alive, 5 report their conditions worse, 8 are improved and 2 are unchanged. No patient was without cardiac complaint.

TABLE XIV.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN COMBINED DERIVATIONS 1, 2 AND 3.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
11 to 20 . . .	1	1	0	1	1	100.0	0	0	0	0	0
21 to 30 . . .	4	2	2	0	1	50.0	1	0	1	0	0
31 to 40 . . .	7	5	3	2	2	40.0	2	0	1	1	0
41 to 50 . . .	9	9	6	3	1	11.1	6	0	5	1	0
51 to 60 . . .	12	10	10	0	9	90.0	1	1	0	0	0
61 to 70 . . .	12	11	8	3	5	45.5	5	4	1	0	0
Total . . .	45	38	29	9	19	50.0	15	5	8	2	0

In the complete series of *T*-wave negativity, regardless of derivation grouping, information has been received concerning 829 patients. Two hundred and thirteen (25.6 per cent.) have died from heart disease (Table XV).

TABLE XV.—CARDIAC MORTALITY IN COMPLETE SERIES.

Derivation.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
1	140	117	83	34	78	66.6	33	10	15	8	0
2	688	487	140	347	46	9.4	420	97	161	162	106
1 and 2 . . .	62	52	39	13	35	67.3	16	1	12	3	1
2 and 3 . . .	171	135	61	74	35	25.9	88	25	37	26	16
1, 2 and 3 . .	45	38	29	9	19	50.0	15	5	8	2	0
Total . . .	1106*	829	352	477	213	25.6	572	138	233	201	123

A group of cases was compiled including those cases in which there was *T*-wave negativity without other electrocardiographic abnormalities except ventricular preponderance. This was done with the idea of excluding disorders of cardiac action known in themselves materially to influence cardiac mortality, especially

auricular fibrillation and flutter, ventricular tachycardia, delayed auriculoventricular conduction, complete auriculoventricular dissociation and arborization block. Of the 559 patients in this group of whose condition we have learned, 92 (16.4 per cent.) have died from heart disease (Table XVI). The cardiac mortality in this group is 9.2 per cent. less than that of the complete series.

TABLE XVI.—CARDIAC MORTALITY. T-WAVE NEGATIVITY WITHOUT OTHER ELECTROCARDIOGRAPHIC ABNORMALITIES.

Derivation.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
1	41	32	21	11	17	53.1	13	4	7	2	0
3	550	394	86	308	33	8.3	349	76	132	141	83
1 and 2	32	29	23	6	17	58.6	12	1	8	3	1
2 and 3	112	86	33	53	17	19.7	61	18	28	15	14
1, 2 and 3	21	18	15	3	8	44.4	7	2	4	1	0
Total	756	559	178	381	92	16.4	442	101	179	162	98

Conclusions.

1. The ventricular complexes of the electrocardiogram are the expressions of two distinct processes, impulse conduction and muscle contraction.

2. The *T* wave is the expression of preponderance of contraction on one side of the line of equipotential (Eyster and Meek).

3. *T*-wave negativity results from alteration in potential distribution from changes in contraction preponderance. Changes in contraction preponderance may result from changes in blood volume and from organic or functional myocardial fatigue.

4. The occurrence of *T*-wave negativity in certain isolated and combined derivations of the electrocardiogram bears a fairly definite relationship to degrees of cardiac damage.

5. The significance of *T*-wave negativity in this series as evidence of heart disease in order of gravity is in (1) combined derivations 1 and 2; (2) derivation 1; (3) combined derivations 1, 2 and 3; (4) combined derivations 2 and 3; and (5) derivation 3.

6. *T*-wave negativity in derivation 2 and in combined derivations 1 and 3 has not been observed in the Mayo Clinic and according to the hypothesis cannot exist. Such negativity would indicate a diffuse iso-electric state of the heart which would mean cardiac standstill.

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ILEAL REGURGITATION, NERVES AND DIET IN THE CHRONIC INTESTINAL INVALID.*

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I. Introduction. Since 1566[1] it has been known there is a structure called the ileocecal valve, and it has been known since 1570[2] that the valvular function of this structure is to prevent the regurgitation of feces into the small intestine. Furthermore, it has been known for ninety-eight years[3] that the active muscular sphincteric function of the mechanism at the distal end of the ileum is to moderate the flow of the contents of the small intestine into the colon.

Actual incompetence of the ileocecal valve was first produced experimentally in 1586.[4] This condition has been recognized as a clinical entity for twenty-three years,[5] and its existence was demonstrated in the human by the bismuth-roentgen method at least eighteen years ago.[6] Yet Cole,[6] writing six years ago, was obliged to bemoan the fact that he was unable to arouse any interest in this subject, even on asking if symptoms might be expected, should a patient be fed colonic contents. Cole, Case and other authorities in roentgen work have recognized a correlation in the degree of ileal regurgitation and the severity of the symptoms complained of by

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the patient, and the probable causative connection between ileal regurgitation and many cases of ileal stasis has frequently been pointed out.

Case,[7] in 1913, reported ileal regurgitation in over 16 per cent. of 1500 consecutive gastro-enterological cases. Cole[8] believes that one might expect to find, with modern technic, perhaps 30 per cent. of ileal regurgitation. Baetjer[9] has stated that it is possible to find as high as 50 per cent. of ileal regurgitation by including every case in which a little of the barium enema can be demonstrated to have entered the terminal ileum. Yet even today almost no one can be found who will take more than the most casual interest in this subject in other than a purely academic manner.

If 30 per cent. of all patients coming for gastro-intestinal examination had regurgitation of food into the mouth all the time, someone would soon have to take interest. In the same way if 30 per cent. of all gastro-intestinal patients suffered from chronic rectal incompetence something would certainly get done about it. Yet just because the junction between the ileum and the colon is unable to cause external annoyance to the patient or his friends, nothing gets done about it. It is easy to create a furor about the appendix or a gall-stone but not about the ileocecal mechanism. Why? Possibly because anatomies pass it over with a few lines of small type, medical schools pass it by in parenthesis and students devote their time to something more obvious. Under these circumstances it is scarcely to be wondered at if the victim of ileal regurgitation turns in disgust from physicians who remain ignorant, more than four hundred years after its discovery, concerning an important anatomic and physiologic structure in order to obtain perhaps a little alleviation of symptoms at the hands of some cult not in the regular profession.

The term ileal regurgitation as here used includes not only regurgitation into the ileum resulting from incompetence of the actual ileocecal protective mechanism but also the condition produced surgically by operative removal of the ileocecal area of the intestine; there is thus produced the same condition of continuity between the colon and small intestine. Two such surgically produced cases of regurgitation are included in the present study. For purposes of treatment both these groups of cases are in the same class on account of their lack of a break in continuity between the large and small intestine.

The objects of this paper are as follows:

1. To draw attention to the fact that too little attention is being devoted to ileal regurgitation, a pathologic condition which is a fact and not a theory.

2. To point out the ease and certainty with which the presence of this condition may be determined.

3. To present for consideration a new diagnostic sign of ileal regurgitation which is at least suggestive in value.

4. To indicate the remarkable frequency of ileal regurgitation in the class of cases referred to as chronic intestinal invalids.

5. To indicate the almost constant coexistence of ileal regurgitation and various forms of excessive nervous irritability.

6. To outline a non-surgical method of treatment which has given a reasonable degree of satisfaction.

7. To record the results of such treatment in a consecutive series of fifty chronic intestinal invalids.

II. DIAGNOSIS. (*a*) Hertz,[5] in 1897, reported a clinical sign the presence of which was considered by him to indicate the existence of ileal regurgitation. Treatment carried out by him on the assumption of the existence of regurgitation apparently gave satisfactory results. His diagnostic procedure was as follows: One hand is pressed deep across the middle of the ascending colon to block possible distal expulsion of gas in the cecum. Downward pressure with the other hand in the direction of the pole of the cecum will then, if regurgitation exists, result in coarse crepitation and perhaps a gurgling noise as the cecal gas is forced back into the ileum.

(*b*) Gas is not usually present in the small intestine. The presence of generalized gas throughout the abdomen suggests a deficient ileocecal mechanism.

(*c*) A cecum and ascending colon dilated with gas combined with a spastic descending colon frequently accompany ileal regurgitation.

(*d*) In the presence of this condition the hepatic flexure and the sigmoid loop are frequently distended by gas.

(*e*) A generalized yellowish discoloration of the skin, especially in the distribution areas affected by Addison's disease, is usual.

(*f*) The eye sign is positive. By the eye sign is indicated a marked dirty discoloration of the whole of both eye sockets. This discoloration is not like other more or less limited discolorations about the eyes with which the writer is familiar. This sign is suggestive, not pathognomonic. It is practically always present, varying in degree with the intensity and duration of the ileal regurgitation. It may be present in the absence of such regurgitation. Should this be the case, however, treatment, as for ileal regurgitation, will cause a gradual disappearance of the sign in the same manner, but more rapidly than is the case when ileal regurgitation has been demonstrated to exist.

(*g*) The usual complaints of the patient with ileal regurgitation are abdominal pain of various sorts, intestinal gas, constipation and nerves.

The pain complained of may be a slight general abdominal discomfort or it may be associated with the presence of gas, particularly in the cecum, hepatic flexure or sigmoid loop, more rarely in the splenic flexure. A second type of pain in these cases is a high central

epigastric pain which often becomes confused with that of gastric ulcer; this particular type of pain is frequently relieved by increase of the costal angle through appropriate developmental exercises. A third characteristic type of pain is a transverse soreness of the abdomen, apparently definitely related to the existence of a spastic transverse colon. A fourth type of pain is that due to distress of the heart following pressure from excessive gas in the stomach, resembling in character the heart pain complained of by the typical neurocardiac asthenic patient.

Constipation is almost universal, being usually of the spastic variety, which in the majority of cases shows definite improvement under the administration of atropine.

(*h*) Diagnosis is absolute by roentgen examination. The presence of a majority of the above signs or symptoms should be sufficient to indicate the necessity for a thorough roentgen examination of the gastro-intestinal tract. This will usually yield more or less negative results if the examination stops short of the administration of an opaque enema, although the previous examination is of value in determining whether the colon is spastic or whether it has become atonic, the latter condition very possibly a later exhaustion stage following the spastic state.

Judging from the relative infrequency with which patients referred to me—often after gastro-intestinal examination by competent roentgenologists—have previously been given an enema, the opaque enema is considered unnecessary; or possibly this omission occurs because, unless it is habitual routine, the administration of the opaque enema is distasteful. There is no doubt, however, that the opaque enema is the most valuable single procedure available today in the study of conditions existing within the colon and at the ileocecal juncture, especially with fluoroscopic observation of the withdrawal or expulsion of the enema at the completion of the usual examination.

In all of the fifty cases here reported the administration of the opaque enema was followed by a study of the filled colon; the enema was then withdrawn, the entire procedure being followed fluoroscopically. Much colon physiology is learned by watching the colon empty itself. If the terminal ileum is filled by regurgitation it usually remains filled until the entire colon empties from cecum to ampulla. The ileal contents thereafter may or may not be seen to follow the course of the colonic contents from cecum to ampulla, the whole distance occasionally being traversed by a block of opaque substance previously in the ileum in the space of a comparatively few seconds. To see a long, ptotic, festooned, loosely attached, M-shaped colon suddenly transform itself into a short omega style colon without evident excess of length anywhere, in order apparently to facilitate the smooth and rapid passage of large blocks of colonic contents, is to get new ideas on whether or not to do frequent fixa-

tion of the colon. Fluoroscopic study of the withdrawal of the opaque enema is certainly too little practised. There is no substitute for this procedure, which if properly carried out is rapid and satisfactory both to the patient and to the observer.

III. Frequency of Ileal Regurgitation On the basis of the observations by Case, Cole, Baetjer and others it would seem that ileal regurgitation may be expected in 20 to 30 per cent. of any series of gastro-intestinal cases. Therefore, if one finds a frequency higher than 50 per cent. in any consecutive series of cases it must be considered distinctly unusual.

In the series of 50 consecutive chronic intestinal invalids upon which this paper is based the existence of ileal regurgitation was demonstrated in 80 per cent. of the cases. Such a high frequency of ileal regurgitation is, to say the least, surprising and calls if possible for explanation.

The technic employed was identical. All observations were made by both Dr. L. B. Morrison and the writer. A large rectal tube was used. The enema was allowed to flow in until the cecum was barely well filled. The flow of the enema was then checked before any evidence of undue distention occurred. No manipulation was indulged in until it had been determined if the barium suspension would be carried back into the ileum by antiperistalsis. Occasionally a half-minute or so would elapse before antiperistalsis became active enough to produce visible ileal regurgitation. Only cases in which antiperistalsis by itself and without external pressure carried the barium back into the ileum were recorded as having regurgitation. On the other hand it may be stated that it was rather unusual to find a case in which factors other than antiperistalsis did cause regurgitation, possibly in view of the precaution taken against overdistention of the cecum. Cases showing regurgitation after changes in position or the strains incident to evacuation of the bowels were not classed as having regurgitation.

After fluoroscopy of the filled colon and the taking of plates as necessary the receptacle containing the enema was dropped to the floor and the emptying of the colon was studied fluoroscopically. This procedure yielded much information concerning colon physiology and cannot be too highly recommended to those interested in gastro-enterology.

In view of the above precautions there is little doubt about the facts in relation to this 80 per cent. frequency of ileal regurgitation in the group of cases studied.

Consequently, it seems necessary to look for some underlying reason for such frequency in connection with the condition of the patients themselves. The inference is that this astonishingly high frequency of regurgitation found in these cases may be considered as a factor worthy of attention in the carrying out of any treatment directed toward improving the general health of the patients presenting this condition.

IV. Frequency of the Existence of Nerves. The complaint of nerves, sometimes of most bizarre type, seems almost constant in the chronic intestinal invalid. In fact, there was but one case in fifty which did not complain of some form of increased nervous irritability or tension. The frequency of this complaint in the series of cases under consideration is therefore 98 per cent. One example is sufficient to indicate the curious manifestations of nerves which these patients may present.

Mr. R. P., sculptor, white, aged thirty-five years, single, height six feet, weight 205 pounds, with good habits, brought up on a Western ranch, was first seen October 7, 1919.

Family History. Father died of cancer of the rectum at sixty-six years of age, family history otherwise negative.

Personal History. Patient lived always in the open, mostly on horseback, until the age of twenty-two. He could always keep up with the others in doing heavy, physical labor, but he "always felt as though he weighed a ton," and never liked exercise, feeling that he always expended excessive energy for the results produced. Patient had measles at eight, mumps severely at fourteen and scarlet fever at sixteen. Otherwise the early history was negative. Patient began to worry about the future at twelve to fourteen years of age, probably on account of the straightened circumstances of the family. He always had a desperate desire to study art, and has been active in sculpture for the last fifteen years.

Present Illness. Nervous, worried easily, gets along, but uses up excessive energy. Has never collapsed, but frequently has difficulty in controlling his temper, and after the close of any strenuous session with students or others is likely to get weepy. Has fainted four times, the last two times after being waked up at night by abdominal cramps. These occasions were one year ago and two nights before first coming for advice. On the latter occasion patient woke up with abdominal cramps, promptly fainted and was not normal for an hour.

Patient complains of a "woozy feeling in the lower jaw" and "a hot spot on the crown of the head, roughly circular in shape, about three inches in diameter, approximately in the position of a priest's tonsure." This hot spot has been present for many months and can be accurately outlined with the finger. The existence of this hot spot has seemed parallel to a decreased efficiency in the power of expression of thought and other forms of mental concentration. Patient has suffered intermittently from coxalgia, this condition having been almost constant for the past few months.

Physical Examination. Physical examination in general negative, the patient being tall, with a large frame and very sloping shoulders. The musculature is at present deficient. Posture fair. Skin negative except for some discoloration, and numerous pimples on the back. Pulse, 65; blood-pressure, 140–90. Eye sign positive.

Gastro-intestinal roentgen examination, beginning October 9, showed a sluggish stomach, with slight pyloric spasm, normal duodenum and normally shaped colon. The ileocecal valve was incompetent, the last one or two feet of ileum remaining filled after the evacuation of the enema. The ileum seemed sluggish in action. To promote possible action the patient was given a half glass of water to drink. Twenty to thirty seconds afterward the terminal ileum was suddenly and completely evacuated, after two definite and very vigorous forward and backward movements of the block of opaque substance contained in the ileum. It was very striking to observe this sudden activity of the ileum apparently as a result of the ingestion of a half glass of water.*

Treatment. Active treatment, chiefly by diet and exercise, commenced on October 11, 1919. Improvement was rapid and continuous. On October 25 the patient reported that the hot spot on the back of his head had been gone for twenty-four hours and that his head was clearer. On October 29 the patient stated there had been no return of the hot spot and that his head was perfectly clear. He said that he had done a hard day's work, during which he had not felt tired as usual. He considered himself cured of his nerves and had no more coxalgia. On November 5 the patient reported that he was "feeling fine." He stated that he was convinced that an excessive use of food had been a serious factor in his condition and that he would hereafter be distinctly temperate both in food and candy. He said that he was very pleased because he had been able to do a real piece of constructive writing for a report which had been accepted as a unanimous opinion by the committee on which he was working. He also stated that this was the first time for nearly two years that he had felt his head to be in good order for intellectual purposes. On December 3 the patient wrote that he was "too well to waste time or money on doctoring."

V. Relation of Ileal Regurgitation to Nerves. Since nerves of some kind were present in 98 per cent. of the fifty cases and regurgitation was present in only 80 per cent. the nerves cannot be said to be always secondary to ileal regurgitation. A study of the 20 per cent. of cases in the series free from ileal regurgitation gives the following results.

The ten chronic intestinal invalids with nerves but with normal ileocecal mechanism were divided between the herbivorous and carnivorous human types[10] in the proportion of 6 to 4. In the herbivorous group, however, one-half the cases had a definite organic lesion, as a possible cause for nervousness. In the remaining herbivorous cases, and in all of the four carnivorous cases, there was no obvious cause for nerves outside the neuropsychiatric sphere. It is probable that overwork, mental worries and fatigue were

* This observation has been repeated, and the procedure outlined has been found useful on numerous occasions since the above was written.

factors in all cases. It is of interest, however, that none of the carnivorous cases had an organic factor. This is directly in line with the results of a study reported by Hodskins[11] concerning human type and the etiology of epilepsy following suggestions by the writer.

As a result of the above it seems probable that ileal regurgitation acts, if at all, only as a precipitating factor, which promotes, possibly through chemical metabolic means, nervous irritability. This is the more probable, in view of the fact that various small forms of superficial nervous irritability disappear rapidly after the application of a diet directed toward preventing the usual undesirable symptoms of ileal regurgitation, parallel with the improvement noted in the functioning of the digestive system. After this comparatively rapid primary improvement, however, there then remains the fundamental irritability of the nervous system, varying with the individual, to be combated by appropriate therapeutic procedures.

VI. Treatment. Treatment is divided into the early, intermediate and late stages of convalescence. In general, during the early stage, the objectives are external and internal rest, varied by carefully controlled periods of exercise. This means that after perhaps a few days of complete bodily rest, if this be deemed essential, the patient, if as usual ambulatory, takes up again his daily life, but with the work periods broken as nearly as possible by five-minute rests every half-hour during the day. This specification is based upon the principle that rest from fatigue is effective inversely according to the duration of the preceding fatigue periods. Internally, rest is obtained by the utilization of the simplest, softest bland diet which can be made satisfactory to the patient. At this time eggs, meat and fish are absolutely contra-indicated, as being potentially putrefactive substances. The duration of the early stage of convalescence covers usually from one week to one month.

The intermediate stage covers perhaps the next two months of convalescence. During this period the diet is gradually amplified and the patient begins to approximate more nearly normal conditions in the manner of his daily work. During this stage it is important to warn the patient that it is impossible to expect continuous recovery. The usual sequence of events is that the proportion of good days to bad increases and that the intensity of the undesirable complaints becomes less. As a rule there will be at least two or three opportunities to demonstrate to the patient the fallacy of his allowing himself full liberty of action simply on account of a sensation of well-being too early in the progress of convalescence. The invariable result of this procedure is subsequent collapse, or at least a definite setback in progress, and there is usually opportunity to prove that a single indiscretion may not be wholly recovered from for as much as one or two weeks. The word indiscretion is applied both to the expenditure of bodily and mental effort and to the excessive use of undesirable foods.

The late stage of convalescence covers from two or three months to a year or more, since if the patient has properly learned his lesson he may continue to improve in a general way over perhaps two or three years. This is a period of active experimentation on the part of the patient. Having learned his lesson it is for him to determine how nearly he can approximate a so-called normal standard of work and then to realize that every excess beyond his own limit must be paid for by a relative return of the symptoms from which he has become free. It is therefore for him to determine whether the emergency justifies the sacrifice which he knows must follow.

There are five totally distinct factors of value in treatment. These are grouped under the following headings:

1. Social.
2. Mental.
3. Dietary.
4. Orthopedic.
5. Glandular.

They are discussed at some length in another paper,[12] three paragraphs from which are here quoted.

"The dietary employed is based in part upon a consideration of the large amount of work by many reputable investigators, which tends to prove the ease with which the intestinal flora can be changed by a modification of diet, also upon a consideration of the fact that ileal regurgitation is an exceedingly common finding in the chronic intestinal type of invalid. Ileal regurgitation was, for instance, demonstrated in 80 per cent. of a consecutive series of fifty chronic intestinal invalids. Eggs, meat and fish, as being potentially putrefactive, are at first absolutely excluded from the dietary and the use of milk is restricted to the amount ordinarily employed in cooking. After a few weeks of complete exclusion of the above foods it is very common to find that the patient's skin is distinctly less muddy. Slowly the yellowish color of the skin is replaced by white and then by pink, a transition which is greatly appreciated by the average woman patient. During this preliminary period of marked restriction of the diet bran and the coarse vegetables are eliminated. No diet list is given, the patients being thus required to use their own brains in the working out of a suitable dietary. One advantage of this system is that the patient gradually acquires an adequate dietary for which he has the least possible dislike. If the dietary actually employed by the patient is written out and continually checked up at successive visits the results seem better from the point of view both of interest of the patient and of the physician, than if a diet slip is handed the patient at the first visit. Eggs, meat and fish are rigidly excluded from the diet for at least one month. During the latter part of this month, however, there is an increasing use of eggs as a flavoring in puddings or other cooked dishes, in which the eggs are finely divided by mixture with the various carbohy-

drates or vegetables. Meat gravies as relishes precede the use of meats as such. During the month of restricted diet, liberal use is made of two special articles of food in conjunction with the usual fruits, starches, vegetables and fats. These two articles are cream cheese (or perhaps the ordinary cheese when used as a flavoring in various cooked dishes) and gelatin. The frequent use of flavored gelatins in the form of salads or desserts is encouraged. The necessary minerals and the water and fat soluble vitamines are provided for by the use of raw fruit and green vegetables and a good grade of butter. In this connection it is surprising to discover how few people are acquainted with the virtues, both from a financial and an economic point of view, of chopped raw cabbage. This food as a salad with French dressing has been taken time and time again without the slightest discomfort or after-effects by patients who had previously stated that they could not possibly eat such a coarse vegetable.

At the end of a month or six weeks if the progress of the patient justifies it—as evidenced by decreased constipation, lessened irritability, lessened disturbance from gas, better appetite and sleep, better color of the skin, and fewer headaches—meat is put back into the dietary at first once a week. The intervals between the days on which meat is used are thereafter shortened according to circumstances. But in the chronic intestinal invalid it has been found most unusual, if meat, eggs or fish as such can be handled with comfort more frequently than two or three times a week. The intermittent use of eggs, meat and fish has another virtue in addition to its economy and its tendency to discourage the growth of undesirable intestinal flora. If the patient has only to wait over one or two days of restricted diet before being allowed a day of full diet, there seems to be much less desire for large quantities of these potentially putrefactive foods, which are handled with difficulty certainly in all patients with demonstrated ileal regurgitation.

In practice, on completion of the history, physical examination and the routine roentgen examination of the gastro-intestinal tract, of which fluoroscopic study of an opaque enema is an essential element, the social and mental factors receive first consideration in the progress of treatment. As soon as these factors are, so to speak, stabilized the diet is taken under serious consideration. In conjunction with diet frequent use is made of mineral oil, agar, yeast and atropin, and every attempt is made to take advantage of habit formation and the natural rectal reflexes. As soon as the diet has become satisfactory the application of orthopedic procedures follow, and finally comes the use of the glandular preparations when indicated. Thus by the end of the first month or so all five of these totally independent factors are being simultaneously employed in the effort to bring about as rapidly as possible an improvement in the general condition of the patient. Belts are rarely used, since

they tend to decrease the faith of the patient in his own ability to carry himself through his day's work. Only slight attention is paid to the question of weight, provided there is not a progressive loss in weight. Not infrequently one may find an apparently healthy person of almost incredible thinness. On the other hand excessive fat is no guarantee of health. Usually, however, the very thin patients will put on at least from ten to fifteen pounds in the course of a few months without apparent effort if otherwise satisfactory progress is being made."

Case,[13] who has devoted serious consideration to this question, has stated that if the ileocecal mechanism is once incompetent it is always incompetent. This is doubtless true in the majority of cases, but not always, as indicated by a case reported by the writer,[14] in which reëxamination at the end of one and two years, of a patient with previously demonstrated ileal regurgitation, proved that the regurgitation was no longer present. Kellog,[15] one of the few persons in this country who has taken ileocecal incompetence seriously, has even advised operation[16] for the restoration of the ileocecal mechanism. Without discussing the actual merits of this procedure it may be stated that in practically all cases satisfactory results in the way of treatment have been obtained by the writer by non-surgical procedure. Numerous cases have been reëxamined at various intervals after treatment. If the ileocecal mechanism is still found deficient it has at least been found to be much less so than at the original examination, and there has also been observed in every case a striking improvement in the general tone and action of the colon. One may therefore say in regard to operative treatment that it is usually unnecessary, since satisfactory results can be obtained without it and in the absence of the risks involved by operation.

VII. Results of Treatment. Application of the method of treatment outlined above has yielded the following results in the consecutive series of fifty chronic intestinal invalids upon which this paper is based.

No improvement	6 per cent.
Improvement	8 "
Improvement plus	86 "
Total improved	94 "

In the group of three cases constituting the 6 per cent. considered not improved is included one case with ileal regurgitation and concomitant diabetes. Treatment was practically refused for fear of upsetting the diabetic treatment. With this case excluded the percentage of cases in which no improvement in the general condition was obtained is obviously lower than 6 per cent. On the other hand the obtaining of a marked or satisfactory degree of improve-

ment in 86 per cent. of 50 cases, makes it possible to speak with some assurance concerning the prognosis, when first asked about this matter by a patient who may be in a state of mental perturbation as a consequence of frequent previous medical failures.

On the basis of the above results it is justifiable to tell the chronic intestinal invalid that he has a better than 90 per cent. prospect of improvement and a better than 80 per cent. prospect of being very much improved as a result of a few months of non-surgical treatment. This applies to the cases in which ileal regurgitation is proved. For the chronic intestinal invalid without ileal regurgitation progress should be proportionately more certain and more rapid.

VIII. SUMMARY. 1. Attention is drawn to the fact that responsible physicians refuse to become interested in a morbid condition with a history dating back to the Middle Ages.

2. The conditions associated with or resulting from ileal regurgitation do not favor optimum functioning of the gastro-intestinal tract.

3. The patient with ileal regurgitation usually suffers from an increased intensity of any nervous irritability to which he may be liable, during the continuance of untreated ileal regurgitation.

4. Immediate treatment of ileal regurgitation is by simple, bland, non-putrefying diet.

5. Adequate treatment must consider every aspect of the patient's welfare.

6. The results of treatment are indicated.

IX. CONCLUSIONS. 1. Ileal regurgitation is not a normal condition. Disregard of its existence does not promote health.

2. The existence of ileal regurgitation may be demonstrated with ease and certainty.

3. In unselected gastro-intestinal material a frequency of 20 to 30 per cent. of ileal regurgitation is to be expected. In a consecutive personal series of 50 chronic intestinal invalids the frequency of ileal regurgitation was 80 per cent.

4. Marked improvement in the general condition of 86 per cent. of this series of chronic intestinal invalids resulted from treatment directed in part toward relief from the results of the ileal regurgitation itself and directed in part toward improving the general condition of the patients.

5. With easy diagnosis assured and the possibility of obtaining satisfactory results by non-surgical treatment sufficiently demonstrated, the physician who prefers to continue to ignore the existence of ileal regurgitation may expect to have his patients suffering from ileal regurgitation take matters into their own hands if they find themselves continued in a medieval status of medical neglect with regard to progressive treatment of their malady.

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THE SIGNIFICANCE OF SMALL AMOUNTS OF SUGAR IN THE URINE.

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and

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new york.

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The clinical interpretation placed upon glycosuria has been subject to a constantly changing point of view for a number of years past. Not satisfied with the mere finding of sugar in the urine, clinical investigators first endeavored to determine the percentage content of the sugar, later the total amount excreted in twenty-four hours and still later by bringing this twenty-four-hour excretion into relation with the carbohydrate intake, they sought to ascertain the balance between this intake and the sugar output. After a time it was observed that not only carbohydrates but also proteins play a part in the production of glycosuria in advanced cases of diabetes, an observation which indicated the need of carefully balancing the total food intake against the sugar output for days and weeks as a scientific basis for diagnosis and therapy.

During this period it was generally understood that the healthy person excretes no sugar and that sugar in the urine is pathologic,

although contributions to the literature made occasional reference to the fact that sugar may appear in the urine of healthy individuals under exceptional conditions.

It also came to be understood that different individuals show a different tolerance to the amount of carbohydrate in their food, and that if this is exceeded there results a temporary or so-called alimentary glycosuria. On the other hand, clinical experience showed that many cases of diabetes remain, so to speak, actively diabetic even though they may show no sugar in the urine, for the apparent reason that renal complications gradually raise the threshold point of sugar excretion.[1] Thus it came to be recognized that the degree of hyperglycemia and the sugar threshold are the determining factors of the glycosuria. The whole problem of sugar tolerance was therefore put upon a more fundamental basis. The blood sugar now came to be recognized as the most important test in diabetes.

Normally the threshold point of sugar excretion is close to 0.16 per cent. blood sugar. Under conditions of health and in the early stages of diabetes it is perfectly safe to regard the appearance of sugar in the urine as an index of the hyperglycemia. In fact, some recent observations lead us to believe that after all this may be the more sensitive method of detecting a lower carbohydrate tolerance provided we have a method sufficiently delicate to estimate the amount of sugar actually present in normal urine.

Recently, Stanley R. Benedict,[2] the originator of the well-known qualitative and quantitative reagents for sugar in the urine, as well as of the most satisfactory method for blood sugar estimation, has introduced a reliable procedure for determining small amounts of sugar in urine. Data obtained with the aid of this method give us a much more correct appreciation of glycosuria, or glycuresis,[3] as Benedict prefers to term it, than we formerly possessed, and it is with this topic that the present paper is particularly concerned.

Although we have long had accurate methods for the quantitative determination of abnormally large amounts of sugar in urine the adaptation of the same methods to the analysis of urines containing small amounts of sugar (less than 0.5 per cent.) has met with only a very moderate degree of success. Since the failure to secure accurate results with urines of low sugar content was due in large part to the interfering action of creatinine, Folin[4] suggested the preliminary removal of this substance by precipitation with picric

[1] Myers and Bailey: Jour. Biol. Chem., 1915, xxiv, 147. Bailey: Arch. Int. Med., 1919, xxiii, 455.

[2] Jour. Biol. Chem., 1918, xxxiv, 195.

[3] Benedict, Osterberg and Neuwirth: Jour. Biol. Chem., 1918, xxxiv, 258. As Benedict has pointed out, glycosuria implies a sudden point at which sugar appears in the urine. Since there is no such point the term is misleading, and Benedict has suggested the term "glycuresis" as indicating an increase of sugar but not a new appearance of sugar in the urine.

[4] Jour. Biol. Chem., 1915, xxii, 327.

acid. With this procedure he demonstrated qualitatively the presence of sugar in normal urine. At about this time one of us[5] was also seeking a satisfactory way of determining the sugar content of normal urine and devised a procedure combining the advantages of Folin's preliminary picric acid precipitation and the well-known color reaction between picric acid and glucose in alkaline solution. This latter reaction had already been used in the estimation of sugar in blood and is easily adaptable to the estimation of sugar in the urine filtrates. Although later work has shown that the figures obtained with this technic are probably higher than the true sugar values, nevertheless the figures show not only the quantity of sugar present in hourly specimens of normal urine but also the effect of glucose ingestion.

Recently, however, work in this direction has been greatly stimulated by the publication of the new Benedict-Osterberg[6] method for the determination of sugar in normal urine. This, too, is a modification of the Lewis-Benedict method for estimating sugar in blood, but possesses a marked advantage over all previous methods in the use of a mercuric nitrate solution for the preliminary precipitation of all interfering substances—creatinine, uric acid, polyphenols and glucuronic acid. By combining the use of this new precipitant with a carefully controlled use of the original color reaction the authors have devised a method by which they can determine what they believe is very nearly the true sugar (reducing carbohydrate) of normal urine. In the experiments reported thus far they do not differentiate glucose qualitatively but simply determine the total sugar and the sugar fermentable by yeast by difference.[7]

In the work reported below we have made use of the Benedict-Osterberg technic essentially unchanged.[8] For the determination of total sugar, however, we have obtained uniformly satisfactory results by using only 10 c.c. of urine and making the subsequent filtrations through small filter papers, but without the aid of suction. In the development of the color we have employed tubes graduated to 15 and 20 c.c. instead of 12.5 and 25 c.c. as suggested by Benedict.

The general plan of our observations was to follow the hourly elimination of sugar for several consecutive hours, both in normal individuals and in those with a lowered sugar tolerance, in order to observe the effect of ingestion of food, the relation of sugar content

[5] Myers: Proc. Soc. Exp. Biol. and Med., 1915–16, xiii, 178.

[6] Benedict and Osterberg: Jour. Biol. Chem., 1918, xxxiv, 195.

[7] Benedict and Osterberg: Studies in Carbohydrate Metabolism. I. A Preliminary Report on the Sugar Elimination in the Urine of the Normal Dog, Jour. Biol. Chem., 1918, xxxiv, 209. Benedict, Osterberg and Neuwirth: Studies in Carbohydrate Metabolism. II. A Study of the Urinary Sugar Excretion in Two Normal Men, Ibid., 1918, xxxiv, 217. For a general discussion of the sugar of normal urine, reference may be made to these papers.

[8] Professor Benedict has recently informed us of a greatly simplified technic which he has developed for this estimation.

to volume and the relative value of the ordinary qualitative test (Benedict's) compared with the new quantitative one. In every case the experiment was started at 10 A.M., since at that hour the assimilation of breakfast was practically complete and the process of carbohydrate metabolism might reasonably be assumed to be at its lowest day level.

TABLE I.—CASES WITH NORMAL CARBOHYDRATE TOLERANCE.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
			CASE	R. T.				
10 to 11 . .	110	—	0.025	28	43	14	57	14
11 to 12 . .	475	—	0.004	19	26	5	74	14
12 to 1 . .	290	—	0.011	32	47	15	53	17
1 to 2 . .	255	—	0.013	33	55	18	45	15
2 to 3 . .	170	—	0.044	75	39	29	61	46
3 to 4 . .	140	—	0.040	56	43	24	57	32
4 to 5 . .	330	—	0.010	36	53	19	47	17
	1770			279		124		155
			CASE	W.				
10 to 11 . .	25	±	0.099	26	46	12	54	14
11 to 12 . .	24	±	0.103	26	65	17	35	9
12 to 1 . .	30	+	0.152	46	76	35	24	11
1 to 2 . .	42	+	0.144	61	82	50	18	11
2 to 3 . .	44	±	0.064	28	61	17	39	11
3 to 4 . .	27	—	0.070	19	63	12	37	7
4 to 5 . .	94	—	0.039	37	59	22	41	15
	286			243		165		78

Case R. T. Dinner at 11.30, consisting of cream soup, mashed potato, lima beans, corn starch, bread and butter, milk

Case W. Dinner at 11.30, consisting of baked potato, cream soup, fish, corn starch, milk.

Table I shows hourly sugar excretions of two patients with normal sugar tolerance. Both of these cases show clearly the gradual increase in the actual amount of sugar excreted after the ingestion of food. Moreover the figures for Case W show the importance of determining the actual number of milligrams of sugar rather than the percentage of sugar excretion. Although the actual quantity of sugar excreted was slightly less than that excreted by Case R. T., yet owing to the relatively small volumes several of the specimens from Case W. gave definitely positive qualitative reactions. Despite this fact, however, the rate of sugar excretion is perfectly normal in both cases, as observation of a large number of individuals would indicate that a normal adult excretes about 1 gm. of reducing sugar in twenty-four hours.

TABLE II.—CASE (L. F.), WITH SLIGHTLY LOWERED CARBOHYDRATE TOLERANCE.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
10 to 11 . .	85	—	0.044	37	49	18	51	19
11 to 12 . .	40	±	0.079	32	19	6	81	26
12 to 1 . .	51	++	0.928	473	65	308	35	165
1 to 2 . .	65	++	0.610	397	78	309	22	88
2 to 3 . .	47	±	0.067	32	59	19	41	13
3 to 4 . .	95	±	0.047	45	44	20	56	25
4 to 5 . .	29	±	0.060	18	44	10	56	8
	412			1034		690		344

Dinner at 11.30, consisting of 200 c.c. of broth, potato, chicken, two slices of bread, rice pudding, 180 c.c. of milk.

TABLE III.—CARBOHYDRATE TOLERANCE OF DIABETIC PATIENT (A. MC W.), MORNING URINE REPORTED "SUGAR-FREE" FOR TWELVE DAYS FOLLOWING TREATMENT.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable Sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
			TEST I.					
10 to 11 . .	140	—	0.015	21	48	10	52	11
11 to 12 . .	340	—	0.010	34	58	23	32	11
12 to 1 . .	45	—	0.046	21	21	5	79	16
1 to 2 . .	22	—	0.085	18	11	2	89	16
2 to 3 . .	92	++	0.820	754	96	720	4	34
3 to 4 . .	60	+	0.148	89	74	66	26	23
4 to 5 . .	360	—	0.035	126	78	98	22	28
	1059			1063		924		139
			TEST II.					
10 to 11 . .	33	—	0.072	24	46	11	54	13
11 to 12 . .	265	—	0.006	22	41	9	59	13
12 to 1 . .	145	+	0.290	420	92	387	8	33
1 to 2 . .	150	+++	2.920	4,370	99	4,332	1	38
2 to 3 . .	145	+++	4.450	6,453	99	6,414	1	39
3 to 4 . .	360	++	0.980	3,528	98	3,449	2	79
4 to 5 . .	535	+	0.320	1,712	95	1,627	5	85
	1633			16,529		16,229		300

Test I. Dinner at 12.30, consisting of 240 c.c. vegetable soup, broiler, stuffed potato, bread and butter, spinach, ice-cream, lady-finger, tea.

Test II. Dinner at 11.30, consisting of baked potato, two slices of bread and butter, cup of custard, 180 c.c. of milk.

That slight impairment of sugar tolerance may easily pass unnoticed in routine urine examinations is demonstrated by Case L. F. Routine specimens taken before breakfast (morning urines) were

consistently reported as negative, but one hour after the ingestion of luncheon the actual sugar excretion rose from 32 mgm. per hour to 473 mgm. per hour. Hourly specimens from 12 until 2 o'clock gave a marked positive reaction, and in a period of two hours there was excreted a total of 870 mgm. of sugar, a quantity almost equal to a normal twenty-four hour output.

These figures serve to call attention again to the well-known but often neglected fact that in diabetes the customary qualitative routine examination of urine is frequently of very little value. These examinations are usually made on a specimen collected before breakfast, perhaps twelve hours after the last meal has been eaten. Under such conditions the urine may show no effect from the last ingestion of food, and the test may give very misleading results.

Such a case is reported in Table III. This patient had been reported "sugar-free" every day for twelve consecutive days. The results tabulated here, however, show that in a single hour after a low carbohydrate luncheon the patient excreted 754 mgm. of sugar, while three hours after a moderate carbohydrate intake the excretion was 6.5 gm.

TABLE IV.—OBSERVATIONS ON F. T., A MILD DIABETIC OF LONG STANDING.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
10 to 11 . .	107	+	0.245	262	83	218	17	44
11 to 12 . .	62	+++	1.660	1030	98	1011	2	19
12 to 1 . .	59	+	0.300	127	87	110	13	17
1 to 2 . .	52	+	0.072	37	59	22	41	15
2 to 3 . .	47	−	0.050	24	33	8	67	16
3 to 5 . .	150	−	0.031	46	50	23	50	23
5 to 6 . .	50	−	0.060	30	43	13	57	17
	527			1556		1405		151

Breakfast at 10 o'clock, containing about 50 grams carbohydrate.

From a clinical point of view the data presented in Table IV are perhaps the most interesting of any we have obtained. F. T. has had diabetes for several years, but on a restricted diet has been "sugar-free." Recently, however, while making the Benedict qualitative test on his own urine he obtained a positive reaction. Similar tests for several successive days gave negative results, but in spite of this he came to the laboratory for blood and urine examinations. At our suggestion he made no change in diet but ate his regular 50 gm. carbohydrate breakfast at 10 o'clock, collecting specimens hourly thereafter. It is interesting to note that during the second hour after breakfast the percentage of sugar was 1.6,

but during the fourth hour it dropped to 0.07 per cent., and after the fourth hour the qualitative test gave a negative result. Obviously in such cases as F. T. the ordinary qualitative test on an occasional specimen may be very misleading.

Further presentation of figures seems unnecessary in order to emphasize the practical value of the work outlined above. The use of the method demonstrates more clearly than ever before the error of the idea that glycosuria is a sudden phenomenon. The elimination of sugar through the urine is a continuous process, quite independent of the volume of the urine, but showing a definite increase after the ingestion of food. This increase in absolute quantity of sugar in the urine, or glycuresis, as Benedict calls it, follows in a greater or less degree the mere process of digestion, although the actual food consumed may contain no sugar whatever.

Along with this deeper conception of sugar excretion the new method affords the clinician valuable aid in the attempt to diagnose and treat cases in which as yet the sugar tolerance is only slightly lowered. Because of the low concentration of the sugar in the urine the old qualitative tests with copper solutions may frequently give misleading results in cases of slightly lowered sugar tolerance, but the use of the new technic on a twenty-four hour specimen makes an accurate determination of the exact sugar output a relatively simple matter. An occasional determination of this sort could scarcely fail to be of far greater value in the treatment of the case than the customary qualitative analysis.

Conclusion. It would appear from qualitative sugar observations on hourly specimens of urine, a few of which are given in the present paper, that the results obtained with the usual qualitative tests made upon specimens of urine taken at random, or even in the morning before breakfast, are quite misleading as regards the carbohydrate tolerance of the patient.

PATHOGENESIS OF ACUTE LEUKEMIA: REPORT OF A CASE OF ACUTE MYELOBLASTIC LEUKEMIA, WITH THE ASSOCIATION OR COMPLICATION OF VINCENT'S ANGINA.

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and

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(From the Department of Medicine, Gouverneur Hospital, Dr. Camac, Director.)

Patient, R. M., nativity, Poland; occupation, operator; aged twenty-six years. Admitted to Gouverneur Hospital, March 7, 1920. Died March 12, 1920.

Family History. Ignorant of conditions of relatives in Poland. Knows of nothing unusual in family.

Previous History. Patient is married. In addition to her household duties she worked daily as an operator in a clothing factory. Usual diseases of childhood. Denies venereal infection. Her health has always been good. She has been married seven months. No pregnancies. Menses regular. No previous attacks.

Present History. Patient was in excellent health until two weeks prior to admission. Her illness dates from a day on which she washed her hair, and before it was dry she went into the street to do her marketing. Shortly after her return there developed a severe headache, and her ears, neck and shoulders pained her. These complaints continued, and shortly afterward she noticed a sore on the mucous membrane of the right cheek. This rapidly spread until it involved the gums of the upper right alveolar ridge and the mucous membrane of the hard palate. Coincident with the extension of the lesion in the mouth there developed a swelling under the jaw, first on the right side and then on the left side. As this swelling increased in size it became difficult for her to swallow or to speak. She cannot state whether she had a fever. She was refused treatment for her mouth lesion at one of the hospitals of the city. A neighbor cared for her, with various mouth washes, until the odor from the sore in the mouth became foul. Patient then sought admission to the hospital.

General Appearance. Recumbent adult; female; pallor marked; face and neck swollen; some difficulty in breathing.

Eyes: Pupils equal and regular, react to light and accommodation. Mouth: Patient breathes through the open mouth; teeth in poor condition; gums slightly congested; no bleeding from gums; there is a foul-smelling, black, membranous exudate, with a well-defined margin on the roof of the mouth extending slightly beyond the midline on the left and continuous with a like lesion on the gums of the right upper alveolar ridge; there are several lesions of similar appearance on the right cheek, the left cheek and the left upper alveolar ridge on its external surface.

Tongue: Slightly swollen; no leukoplakia or other lesions.

Throat: Swelling of right peritonsillar tissue; right tonsil prominent but is free of exudate; pain and fluctuant sensation elicited pressure over the right antitonsillar pillar; there is inability to separate the jaws more than three-quarters of an inch.

Neck: Painful, massive and conglomerated swelling of submaxillary lymph nodes on both sides, the right more prominent than the left.

Heart: No enlargement; no thrill; no abnormal impulse; rate increased; no murmurs; sounds feeble.

Arteries: Negative.

Pulse: Tension fair, quality poor.

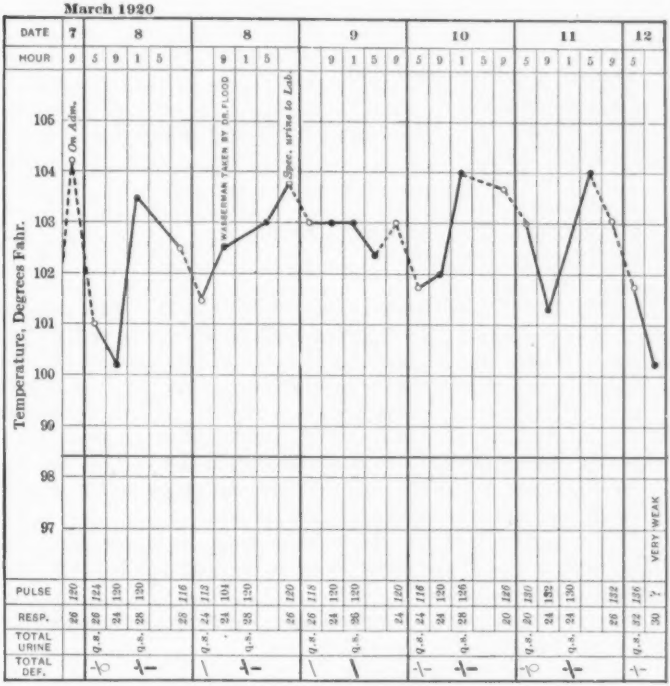
Lungs: Slight dulness; cogwheel breathing at right apex posteriorly; clear and resonant elsewhere.

Abdomen: Scaphoid; no rigidity; no masses.

Liver: Not enlarged.

Spleen: No enlargement made out on percussion and palpation.

Kidneys: Not felt.



Skin: Pronounced eczema of scalp; numerous small hemorrhages along hair line of forehead.

Skeletal Structures: Negative.

Lymphatic System: Discrete and shotty enlargement of postcervical, epitrochlear and inguinal lymph nodes.

Reflexes: Present and active.

CLINICAL PATHOLOGY.

March 8, 1920. *Urine.* Transparency, cloudy.

Color, amber.

Reaction, alkaline.

Albumin, heavy cloud. Glucose, 0.

Stained smear of mouth lesions shows many spirilla and fusiform bacilli.

Acetone, 0.

Casts, many.

Leukocytes and pus, few white cells.

March 8. Culture of mouth lesions negative for Bacillus diphtheria.

BLOOD EXAMINATION.

March 9, 1920. Leukocytes, 190,000.

Number of cells counted, 300.

Polynuclears, 290.

Transitionals, 15. March 10, Wassermann negative.

Lymphocytes, 26.

Myelocytes, 18.

Myeloblasts, 10.

Hb. per cent., 60. Instrument, Sahli.

Erythrocytes, 2,950,000.

Normoblasts, 2.

March 12. Blood smears, reported by Dr. L. Unger, showed nucleated red blood cells together with anisocytosis and poikilocytosis. There is a tremendous increase in the number of white blood cells, which are chiefly myeloblasts. One per cent. myelogenes, a forerunner of the myeloblast is present. A large percentage of the myeloblasts show evidence of considerable degeneration. In the body of some myeloblasts an erythrocyte is seen. This ingestion of erythrocytes is evidence of the terminal stage of the disease. A small percentage of myelocytes are present.

The smear stained for the oxidase reaction is positive. The differential count of the white blood cells on March 10, 1920, date of death, were as follows:

Polymorphonuclears: Neutrophiles, 3 per cent.; eosinophiles, 0 per cent.; basophiles, 0 per cent.

Small lymphocytes, 3 per cent.

Large lymphocytes, 0 per cent.

Myeloblasts, 90 per cent.

Myelocytes, 3 per cent.

Myelogenes, 1 per cent.

Anisocytosis, moderate.

Poikilocytophilia, moderate.

Polychromatophilia, none.

REPORT OF SOCIAL SERVICE INVESTIGATION.

Home of patient fairly clean; no stove in rooms; patient did cooking on neighbor's stove; patient and husband worked during day; neighbors state that their food was apparently adequate and of good quality.

March 8. Patient examined by nose and throat consultant. Suspicion of scorbutus. Findings: marked necrosis of the lower jaw. Severe tenderness on pressure over the right canine fossa.

March 9. Patient breathing easier; less apathy; no improvement in mouth lesions.

March 11. Patient much weaker; takes no food; marked inspiratory dyspnea.

Diagnosis: Acute myeloblastic leukemia.

Treatment: Consisted of arsphenamin locally to mouth and intravenously.

When one has the opportunity of studying a case of acute leukemia he must necessarily be impressed with its peculiarly infectious-like type of onset and course. Yet strange as it may seem to him the conclusion that acute leukemia is an infection has been held as untenable by a number of competent investigators.

Since the day of Newman, who in 1870 showed the marrow lesions in leukemia, the contention of Lowitz, who held that leukemia was a disease of the blood itself, has been discarded. Although the bone-marrow, and especially the lymphoid tissue of true bone-marrow, has been accepted as the principal affected tissue, yet the exciting cause is still surrounded with a great deal of uncertainty. The widespread occurrence of leukemia in all animals, according to Warthin, speaks against infection and corresponds to a neoplastic growth. One cannot help wonder if it is a tumefaction or a sarcomatous condition (Banti), why the condition does not progress in a steady advance and why the blood does not correspond to the condition. The peculiar remissions which occur so frequently do not correspond to the usual course of a tumor. The spontaneous *bona fide* cases of cure, which occur in myeloblastic leukemia, again seem to us to oppose the theory of tumefaction. A white blood count under 25,000, notwithstanding the number of myelogenes, myeloblasts or other cells, augurs well for the patient, and a cure in such instances can at least be hoped for.

Although no specific organism has been satisfactorily demonstrated as the etiologic agent in leukemia, still there has been quite an accumulation of corroborative evidence that the basic factor in its production must be an infection.

Ellermann and his co-workers in Copenhagen claimed to have produced either myeloid or lymphatic leukemia or an anemia without leukemia in chickens by means of a filtrable virus. Although his work has been impressive, still others and very competent workers were unable, with practically the same technic to produce his results. It is well to recall here that chicken leukemia is not exactly like human leukemia for chickens do not have lymph nodes, with the exception of the cervical region, and this corresponds histologically to the thymus in the human. Clinically therefore we would not have any lymphatic swellings, an important sign in true leukemia.

The literature abounds with other claims of certain bacteria producing the lesion. Cabot presents an interesting contribution but not conclusive by any means, because of the dangers of coincidence, of a nurse who became a victim of leukemia while nursing a leukemic patient. Again, there have been the stories of the epidemic of leukemia, one in the valley of Enz in 1905 and another in Toulouse in 1912. The stories of these epidemics can hardly stand the light of day, as the record, for instance in Toulouse, of 18 cases of all classes of leukemia in twenty-two months wherein previously leukemia was very rare in this region, counts very little as a bullet-proof conclusion.

In rebuttal of their evidence and thinking from an infectious standpoint, it is rather hard to reconcile the incontrovertible proofs of cases wherein a number of leukemic mothers have given birth to healthy children. There are at least a dozen of such instances in the literature.

There is no question that the clinical symptoms, such as the temperature, swollen spleen, hemorrhagic condition of the mouth, tonsils and intestinal symptoms, would make one favor an infectious origin, but in leukemia we have so many secondary invaders that it is difficult to recognize just what symptoms are really leukemic and just what are due to a secondary invader.

Dorothy Reed, in her opinion, has summed up the evidence very tersely when she says that it is due to some chemotaxis in some part of the body, with a peculiar predilection for myeloid tissue.

Packard and Ottenberg have described a peculiar leukotoxic state in the lymphatic variety.

Bearing upon our own work it is well to recognize that in lymphatic leukemia about one-tenth of the leukocytes are absolutely in a degenerative state, and in one case reported by Emerson the leukocytes would not stain at all.

It is interesting to note that Rotky, in 1900, stated that the blood in leukemia has no agglutinating power to bacteria and that, to my mind, not only explains the apparent incapacity for production of antibodies, but also explains the lack of resistant power in leukemic patients to otherwise harmless infections. Again, it gives us a practical clue to the number of bacteria which have been brought forward as the specific etiologic agent.

Sondern, in a personal communication (although he feels that he is not quite justified to report this) feels that in a number of instances Vincent's organisms might have been the exciting factor. He has found Vincent spirillum and the fusiform bacillus in twenty-two cases, and in two cases he is convinced that it preceded the leukemia and was the important agent in causing the condition. In two other cases he has had a lymphemic state with over 95 per cent. of lymphocytes. In one case of a child, nine years elapsed before the blood returned to normal and in another case an interval of five years before the blood again became normal.

Again and again I am seeing severe lymphemias with symptoms of leukemia, which after a time proceed to get well so that we necessarily hesitate now and then to give a hopeless prognosis as one ought to if he were absolutely certain that he was dealing with leukemia.

In the army Vincent's angina was considered a very harmless infection. It was found most often in trench mouths. But in our experiences when it is associated with leukemia it is a most potent factor in producing an early death.

To summarize then the complete story of the etiology, leukemia still has an unfinished chapter. The evidence in favor of an infectious theory is rather preponderating, but still far from conclusive. The best we can say as to its causation is to requote Dorothy Reed, when she concluded that it is due to some chemotaxis, with a special predilection for the bone-marrow.

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THE CONTENTS OF THE STOMACH: ITS STUDY AND INTERPRETATION.

By Elbridge J. Best, M.D.,

San Francisco, Calif.

By glancing through the literature one sees the wide acceptance of the small tube as a means of removing the stomach contents by the fractional method, thus enabling one to study the activity of the stomach continuously over a period of hours. Although used by Europeans as early as 1912,[1] it was first brought to the attention of

the American profession by Rehfuss[2] in 1914, who later enlarged upon the benefits to be gained by the "fractional" study of the stomach contents. Our knowledge of the stomach activity as well as our ability to diagnose pathologic conditions has increased thereby manyfold. Much constructive work has been done by Crohn[3] and others. Yet the impression one gets from the literature is that each worker has many little points in technic and methods of procedure that differ from the others and which are never clearly explained in print. For that reason it seems wise to state our method of studying the stomach contents in the clinic in an attempt to keep this phase of stomach examination more uniform and possibly promote wider discussion and use.

The procedure is as follows: The evening before the test the patient is instructed to eat two or three prunes or raisins before retiring. He appears at the clinic at 8 A.M., having taken nothing since the night before. A Rehfuss[2] tube is passed and the contents of the fasting stomach completely removed, measured and examined. The technic of introducing this tube was described in a former paper,[4] from which I quote: "This is done by having the patient open his mouth and say 'Ah.' " The metal tip is dropped behind the tongue and the patient swallows. To prevent gagging and retching the patient takes deep breaths. When this is done the tube can be passed to the 50 cm. mark with hardly an unpleasant sensation to the patient. When down the tube is kept to one side of the throat and causes very little annoyance. During this period the patient can talk, read or devote his attention toward any minor employment to pass the time. Saliva is frequently abundant. The patient is instructed to spit this out, not to swallow it." The tube is removed and the patient is given an Ewald test breakfast. (An oatmeal gruel is used by Crohn, given with the tube still in place. Others, I have learned, feed the gruel through the tube. However, if one wishes to reach as nearly the normal secretion as possible, it seems logical to avoid having a tube interfering with mastication or depriving the patient of the stimuli of taste and chewing. It seems a small but very essential point to bear in mind the physiology of the digestive secretions as is demonstrated by the works of Pawlow[5] and Boldyreff.[6] Also I have determined the HCl deficiency of the oatmeal gruel and find it quite the same as that of bread and water. I therefore feel the advantage lies with the simple bread and water meal which demands definite mastication.)

One-half hour following the beginning of the meal the tube is again introduced and 3 to 5 c.c. of contents removed. This is repeated every fifteen minutes until the two-hour period. At that time all the contents is removed, measured and tested. Each time the sample is withdrawn I insist on a little air being blown back, both before and after, to assure the purity of each specimen.

Such a procedure gives us abundant information. Motility, re-

tention, hypersecretion, presence or absence of normal and abnormal acids and ferments, bleeding, presence of pus or exfoliating gastric mucosa, abnormal albumin and malignant cells can be determined.

In the contents of the fasting stomach the presence of prune or raisin skins speaks for retention. Normal stomachs twelve hours after a meal contain less than 100 c.c. of contents. Over this amount is found in retention and hypersecretion cases. The concentration of acid varies greatly from no free HCl and low total to very high acid which may be almost pure HCl. The presence of bile in these specimens is quite normal. One of the most important items in the study of the fasting contents is that of the microscopic elements. Here we look for pus and blood cells, the character of the gastric epithelial cells and the presence of cells with mitotic figures representing malignancy, which incidentally are very rarely seen. The cells are studied in the fresh and stained preparations. Yeasts and flagellates may be found or Boas-Oppler bacilli may be seen when present. For the more complete study of the microscopic elements, as described by Leoper and Binet,[7] while the tube is in the stomach one can introduce 30 c.c. of normal salt solution and immediately withdraw it, centrifuge the fluid and study the sediment in the fresh and stained condition. When malignancy may be suspected, modifications of the Wolff-Junghaus and allied tests can be carried out for the presence of abnormal albumin and proteolytic ferments.

The removal of only a few cubic centimeters of stomach contents, during the two-hour observation, is to prevent one from removing too large a quantity each time and thus interfere with the stimulation of the meal on the stomach secretion. Also by using 1 c.c. of content and titrating with $\frac{1}{100}$ normal sodium hydrate the buret reading gives the same figure as the use of 10 c.c. of content and one-tenth normal sodium hydrate.

For studying the presence of the ferments in the patients who show no free HCl during the two-hour period the one-hour specimen is selected, filtered and incubated with coagulated egg-albumen as is ordinarily carried out.[8]

After having determined, by titration, the amount of tenth normal hydrochloric acid and total acid in 100 c.c. of the fasting contents and in the fifteen-minute samples over the two-hour digesting period to properly study the findings obtained it is necessary to plot curves, using the acid values as ordinate and the time as abscissa, which portray the actual progress of the acid concentration. In other words, we graphically visualize the ever-changing chemical condition as it exists in the stomach during that period of digestion examined. The advantage of these curves in its superiority over the older "one sample test" that a few clinics still persist in using, is comparable to the advantage of the moving picture over a single snapshot.

These curves may or may not be of great value, depending upon how they are interpreted. Many clinicians, having expected to obtain direct conclusions from the actual acid values, have become discouraged with the fractional method and labeled it as quite

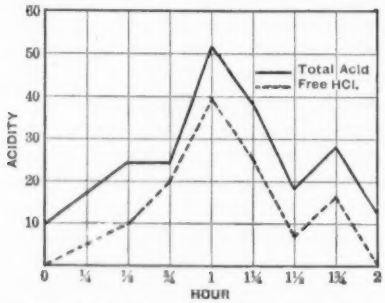

FIG. 1.—Type I, "normal," fasting content 25 c.c.; apex in one hour; one and a half-hour drop, with recovery in one and three-quarter hours seen in duodenal regurgitation.

unessential. The actual acid values mean very little. The shape of the curve means more. There are a few valuable points to look for in studying these curves: (1) Note the acidity of the fasting contents; (2) the apex of the curve; (3) the position of the curve in two hours; (4) the position of the HCl curve compared to the total

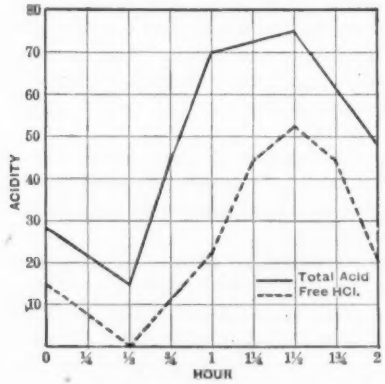

FIG. 2.—Type I, fasting content 50 c.c.; a slight variation between free and total acid curves but the shape is very similar; apex in one and a half hours.

acid curve, that is, whether it follows the total curve regularly or takes an independent and very irregular course.

There are five more or less general and distinct types of curves in which any fractional result will fall. By keeping these five types

in mind and placing the curves received in their proper group a definite knowledge of the secretory and motor activity of the stomach is obtained which becomes a positive item to aid in diagnosticating the condition at hand. Type 1 (Figs. 1 and 2) begins with a moderate fasting acidity and rises to the apex in from one to one and a half hours and a steady decline. The apex may be 60 for total acid or 90. The free HCl curve follows total regularly and about twenty points below. This is considered the normal type.

There may be breaks in the smooth continuity of the curve with large sudden drops in acidity, free and total acid acting parallel. Bile may be present with these drops. Such defects in the regular outline are due to a reflux of duodenal contents into the stomach

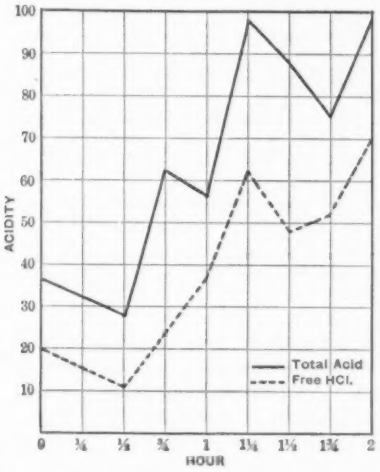

FIG. 3.—Type II, "ascending;" fasting content 50 c.c.; curves slight and irregular: but respond similarly; high point in two hours; mucus +; gastric cells +; diagnosis: duodenal ulcer, with recent hemorrhage.

and are quite a normal event, as demonstrated by Boldyreff.[9] If blood is discovered with such duodenal regurgitation it is the one definite evidence of pathology in the duodenum (Rehfuss[10]).

The second type of curve (Figs. 3 and 4) frequently has a high fasting acidity, a quick drop occurring early after the test-meal and a steady rise to the two-hour period. This is an ascending type of curve frequently showing the HCl steadily approaching the total acid curve until at the two-hour period the stomach content may be almost pure HCl and of a value near 100. This type is found in cases of gastric ulcer of not too long standing, frequently in duodenal ulcers, in recent gall-bladder infections and sometimes in subacute or chronic appendicitis. One cannot say, upon looking at a curve

of this type: "Here is a case of duodenal ulcer," but it does represent the existence of a definite abnormal condition, namely, a marked

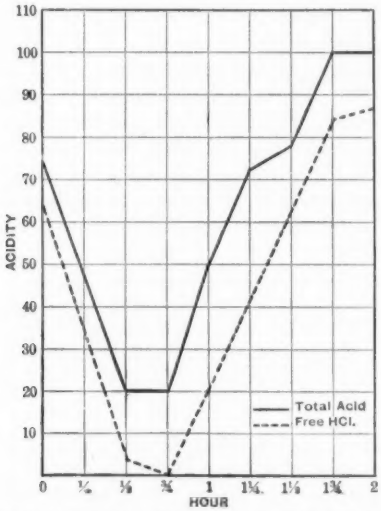

FIG. 4.—Type II, fasting content 50 c.c.; few gastric cells and leukocytes; high fasting, acid; sudden drop with meal and steady, rapid rise to apex in two hours; diagnosis: cholecystitis.

hyperactivity of the gastric secretory apparatus (McWhorter[11]). This hyperactivity usually extends on to the next meal. Sometimes the apex is reached in or before one hour and from that point on the curve becomes almost a horizontal line, with occasionally the appearance of a sudden drop and quick recovery to the former level.

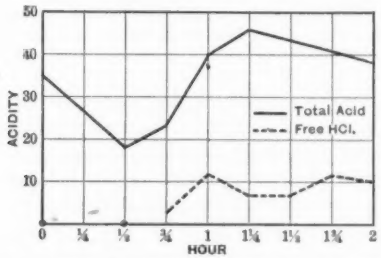

FIG. 5.—Type III, "irregular," fasting content 40 c.c.; mucoid; leukocytes +; free HCl, early absence, later low; irregular compared with total curve; total fairly normal shape; diagnosis: subacute gastritis.

The third type (Fig. 5) shows a total acid curve of possibly normal or low value, taking a fairly normal course, but with the HCl curve

very irregular and not in the least symmetrical with the total curve. The difference between the HCl and total acid values is usually over 20. Such a curve is found in cases of subacute gastritis of not too long duration or in conditions that tend to depress gastric secretion, such as chronic infective processes located at distant points, as for instance the mouth, gall-bladder and appendix. We are dealing here with a depressing influence on the secretory mechanism, possibly in some cases a direct damage to the gastric cells. We are helped, in the microscopic examination of the fasting contents, by the presence of pus, the mouth being above suspicion, or eosin-staining gastric cells, which reveal an inflamed condition of the gastric mucosa. We find cases of marked gingivitis when purulent material is expressed from between the red, swollen gums and the teeth and a curve of type three, the fasting contents showing many pus cells and squamous epithelial cells. It is reasonable to suppose there may be some local inflammatory condition of the gastric mucosa, but, without the presence of increased numbers of gastric cells, the conclusion is that the mouth infection is primary. In such cases a visit to the dentist for scaling and polishing the teeth will result in a large percentage of cures.

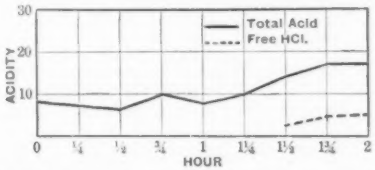

FIG. 6.—Type IV, fasting content 50 c.c.; leukocytes ++; epithelial cells +; no free HCl until late; total curve low; diagnosis: chronic gastritis and esophagitis.

The fourth type (Fig. 6) is really a progression of the third type. Here the total acid is moderately low, with a very low irregular HCl, reaching zero in one or more intervals during the two-hour period or only appearing in one or two samples. Such a curve is found in a chronic gastric inflammation of long standing, in focal infection with systemic reaction, including tuberculosis and lues and in cases of malignancy. With the last-named condition one is helped at times by finding, in the microscopic elements, cells containing mitotic figures.

The fifth type (Fig. 7) is a curve showing the total acid as having a value of about 10, holding mostly to a straight line. No HCl is discovered at any time. All of the samples look like a mixture of bread and water, with possibly the addition of considerable mucus. The ferments are entirely absent. With this curve we have the typical findings in achylia, which is not a disease but purely a manifestation of a deeper seated process. Achylia has been con-

sidered more in detail in a recent paper.[12] It is rather rare to find this curve in gastric malignancy but is seen no less rarely in malignancy elsewhere.

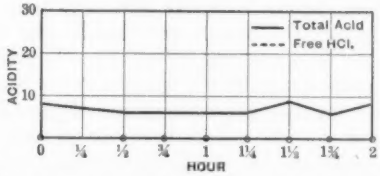

FIG. 7.—Type V, fasting content, 20 c.c.; mucus +; square epithelial cells ++; leukocytes ++; ferments absent; no free HCl; total curve a straight line under 10. This was a case of badly infected mouth and pulmonary tuberculosis.

There is one other form of curve (Fig. 8) occasionally seen in which the total acid is very low and no free HCl is found during the first hour, while the second hour result is definitely normal or similar to type 2. In this instance we are dealing with a psychic secretion (Rehfuss) during the first hour, showing inhibitory effect of nervousness, caused by the first introduction of the stomach tube, whereas in the second hour the chemical or normal secretion appears, uninfluenced by external factors. Such a curve should be repeated, at

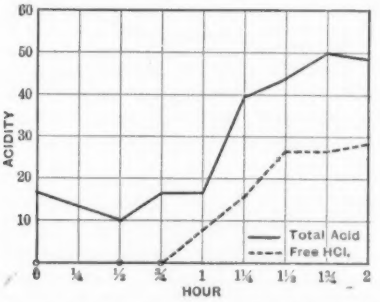

FIG. 8.—"Psychic curve," no free HCl and low total first half of period, then rapid recovery to fairly high values. Patient thin and nervous. Result of second test similar to Fig. 1.

which time one receives a normal curve complete for the two-hour period.

Should a curve look unusual on the first day it is very advisable to repeat the examination once or twice. A steady type of curve will then be obtained which gives the secretory picture for that patient.

In many instances it has been a great help in realizing just how the free HCl curve varies in its progress from the total acid curve, to plot, in a different color, a curve for the difference between the

free and total acids. Normally, such a curve should be a straight line. Marked irregularity and unusual distance from 20 spells disturbance in HCl secretion. I have not been able to determine anything more specific in its interpretation.

Regarding the amount of secretion recoverable from the stomach two hours after the meal was begun, insufficient number of normal cases have been examined to draw conclusions. It would appear that over 100 c.c. of content definitely indicates a delay in emptying or an excess of secretion. This two-hour content usually contains but a small amount of starch, indicating most of the meal has passed the pylorus. The evidence of delay found in this last specimen, including the presence of over 100 c.c. of fluid, has been found to parallel the six-hour retention seen in the roentgen-ray examination.

Summary. A method is outlined for the fractional stomach examination which makes it possible to complete all the tried tests of gastric study in two hours and gives connected pictures of the secretion during this period. The procedure is simple and can be carried out by any practitioner with the aid of his nurse. The gastric curves are placed in five groups, no stress being laid on the actual acid figures, but emphasis is placed upon the position of the apex and the two-hour level of the curve, the difference between the free and total acid curves and the behavior of the free HCl curve. By repeating an examination a more stable, reliable curve is obtained. By carefully following out the above procedure it is possible to become more intimately acquainted with the detail of gastric activity, thus making it possible to carry out treatment by diet and medication in a more intelligent manner as well as making diagnoses of gastric complaints more accurate.

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REVIEWS

DISEASES OF THE NERVOUS SYSTEM. A Text-book of Neurology and Psychiatry. By SMITH ELY JELLIFFE, M.D., PH.D. and WILLIAM A. WHITE, M.D. Third edition. Pp. 988; 470 engravings and 12 plates. Lea & Febiger. Philadelphia.

THE third edition of the work of Dr. Smith Ely Jelliffe, of New York, and Dr. William White, of Washington, D. C., is constructed essentially on the same lines as the former two editions. The book is divided into three parts:

Part I deals with what the authors call the "Physico-chemical Systems," essentially vegetative and visceral neurology and the endocrinopathies. The recent advances made by study and research into the realms of the hormonopoietic system and vegetative neurology are incorporated into this chapter, and add much to its value. In it the authors endeavor to demonstrate more clearly the intimate relationship existing between the so-called ductless glands and the physiologic and pathologic processes in all the systems of the body, whether they be nervous, alimentary or bloodvessel. Many excellent illustrations and diagrams help to clarify this rather obscure subject for the student reader.

Part II is devoted to the "Sensorimotor Systems," being mainly organic neurology. The various observations on living pathology which the great war afforded are judiciously used to augment this chapter. Peripheral nerve injuries and gunshot wounds of the brain and spinal cord are illustrated by many photographs and diagrams.

Part III deals with the "Psychical" or "Symbolic" systems. The principal additions to this part are the articles on the War-neuroses and so-called "Shell-shock." An endeavor is made to show the relationship existing between the neuroses and the psychoses and to demonstrate the mechanism involved in the causation and growth of these disorders. Psychoanalysis, discussed in the opening chapter, is prominent throughout all of part three, and in the treatment of most of the volume the Freudian teachings can be discerned.

Altogether the third edition is much wider in its scope than its predecessors and the facts which the authors have endeavored to emphasize, namely, the interrelation and interdependence of the various divisions of the subject upon each other, are more clearly portrayed than in the second edition of 1917. F. H. L.

THE DIAGNOSIS AND TREATMENT OF HEART DISEASE. By E. M. BROCKBANK, M.D. (Vict.), F.R.C.P.; Hon. Physician, Royal Infirmary, Manchester; Lecturer in Clinical Medicine, Dean of Clinical Instruction, University of Manchester. Fourth edition. Pp. 154. New York: Paul B. Hoeber, 1920.

THIS volume is the outgrowth of *Heart Sounds and Murmurs*, published in 1911, which was limited to cardiac auscultation. The new volume, though larger by 100 pages, is still in "pocket-book form," which makes it handy for the student's use. The first 120 pages are devoted largely to the information to be derived by inspection, palpation, percussion and auscultation in normal and especially abnormal hearts. The emphasis laid upon the insidiousness of endocarditis in children is commendable. The chapter on treatment is well considered. The medical student will find much solid information in small compass in this volume. The more mature student of cardiac disease today will prefer a volume wherein more space is given to the study of abnormal myocardial function. J. E. T.

PHYSICAL BASIS OF HEREDITY. By THOMAS H. MORGAN, Professor of Experimental Zoölogy in Columbia University. Pp. 305; 117 illustrations. Philadelphia and London: J. B. Lippincott Company.

OF the recent advances in the study of heredity and Mendelism, none have been so productive in results as the experimental work of Professor Morgan and his colleagues. About ten years ago they began work with Drosophilia, the little fruit fly, and this form has turned out to be the most favorable yet utilized in the study of heredity. In Drosophilia they have already found several hundred factors which exhibit Mendelian segregation; its chromosomes are distinct and few in number; it is both hardy and prolific; it is easily handled in the laboratory, being reared in pint bottles and fed on small pieces of ripe fruits. These advantages have been utilized to the full and the author believes that, as a result, some of the basic problems of heredity have been solved. In fact the opening statement in this book is: "That the fundamental aspects of heredity should have turned out to be so extraordinarily simple, supports us in the hope that Nature may, after all, be entirely approachable. Her much advertised inscrutability has once more been found to be an illusion due to our ignorance." The book deals with both genetics and cytology and the main thesis is the chromosome theory of heredity. According to this the chromosomes form the material basis of heredity. The various factors,

upon which the manifestations of characters depend, are resident in the chromosomes, whence they influence the nature of the cells and of the organism which the cells collectively build up. The six principles of heredity are discussed in the light of our present knowledge of the chromosomal mechanism.

Due recognition is given the valuable work of Carothers on the mechanism of assortment and that of Wenrich on crossing-over and the linear order of the material of the chromosomes. The involved portions of the discussion will appeal more to the specialized student of this subject, but there is much of interest to the general scientific reader. Those interested in the study of genetics will look forward to reports of the work being done this year in California by Professor Morgan and his associates.

W. H. F. A.

FUNDAMENTALS OF HUMAN ANATOMY. By MARSH PITZMAN, A.B., M.D., Professor of Anatomy in the Dental Department of Washington University, St. Louis. Pp. 356; 101 illustrations. St. Louis: C. V. Mosby Company, 1920.

THIS is an attempted compromise between the compend and the modern standard anatomies, which the author describes as having grown into encyclopedias of our entire anatomic knowledge of the human body. He thinks the rank and file of practitioners of medicine show an unfortunate lack of knowledge of and interest in anatomy, and ascribes this to the attempt to teach too much detail, which results only in confusion. So he has essayed to show his own idea of a modern text-book of human anatomy.

The main point is that only those things are included which it is likely the student will remember. For instance the brachial plexus is given in half a page, and it may be contended that that is all even a fourth-year undergraduate can still retain. Still, as the author advises recourse to the drawings and plates of the larger anatomic works, one cannot be sure that he thinks that this book contains all the student should know. This book is interesting as showing one man's method of teaching anatomy to students who are beginning the study of this subject, and, undoubtedly, if more professors of anatomy would write out their actual methods of teaching it would make for the progress of anatomical pedagogy.

W. H. F. A.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Studien zur Kriegsnephritis (Studies on War Nephritis).—THANNHAUSER (*Ztschr. f. klin. Med.*, 1920, xcviii, 181). This article is a report on 800 cases of acute nephritis. 78.3 per cent. were edematous, 18.6 per cent. edema free and 3.1 per cent. had an edemaless nephritis following a specific infectious disease. The disappearance of the edema was rapid in 60 per cent. and slow in 40 per cent. A characteristic feature of war nephritis is the presence of pulmonary edema dependent on an edematous tendency and not on cardiac insufficiency. Bronchitis was rare but dyspnea was nearly constant at onset. Diuresis was produced by limitation of fluid and salt intake and occasionally by the use of diuretics and digipuratum. Skin drainage of 1000 c.c., often initiated marked diuresis. Fever at onset was very rare. The blood-pressure was high in nearly every edematous patient. With the disappearance of the edema the pressure reached normal. In the non-edematous patients hypertension was present in 65 per cent. The hypertension is almost without exception transient and bears no relation to the non-protein-nitrogen values. Slight cardiac enlargement with loud second sounds was not uncommon when marked dyspnea was present. Albuminuria in the early stages of the disease often reached 20 gm. After the disappearance of the edema more than a trace is unusual. Hematuria is a constant symptom. The specific gravity was high during the oliguric periods but sank when diuresis set in. Changes in the fundi were observed in only two instances. Uremic-eclamptic attacks occurred in only 2 per cent. of the cases, always just after the beginning

of the diuresis. The mortality from acute nephritis was 0.25 per cent. During the grippe epidemic, however, 10 patients, or 4.5 per cent., died. The remainder of the report concerns itself with the problem of edema, and the author concludes that "simultaneous with injury to the kidney injury to the mechanism which regulates salt and water exchange between tissue and blood occurs. Through the summation of these insults edema occurs."

Amyotonia Congenita and Spinal Muscular Atrophy.—KNOX and POWERS, in an article entitled "Three Cases of Spinal Muscular Atrophy, Probably of Werdnig-Hoffman Type" (*Southern Med. Jour.*, 1920, xiii, 86), report on three instances of familial occurrence of muscular weakness in young children. The most striking symptoms were marked paresis of muscles of extremities, especially in the proximal parts, and diminution or absence of the tendon reflexes. The sphincters and muscles of deglutition were not involved. Sensation seemed normal. Two of the patients died before the third year. Unfortunately pathological study was not done. Brief mention is made of autopsy reports of other observers. As a complement of this paper an exceedingly interesting article by Krabbe, entitled "Congenital Familial Spinal Muscular Atrophies and Their Relation to Amyotonia Congenita" (*Brain*, 1920, xliii, 166) has appeared. He failed to find any instances of amyotonia congenita in adults, possibly because those who had the disease were either dead or well. He believes, therefore, that Collier is correct in assuming two different diseases in infants which may be very similar. One is amyotonia congenita and the other progressive muscular dystrophy. These two diseases differ, as shown in the following grouping: (1) Amyotonia congenita is a benign, non-heredofamilial malady with hypotonia, hyperreflexibility and weakness, but without muscular atrophy. The patients recover. (2) From this true amyotonia congenita must be separated certain reported atypical cases and also the cases which, at autopsy, showed atrophy of anterior horn cells and muscles. This group comprises the true muscular dystrophies of infancy of which the Werdnig-Hoffman type is best known.

SURGERY

UNDER THE CHARGE OF

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Lung Abscess from a Practical Surgical Point of View.—WHITTEMORE (*Surg., Gynec. and Obst.*, 1920, xxxi, 144) says that although medical books give lobar pneumonia as the most common etiology of lung abscess in his experience it has seldom if ever been the cause. The

most common cause in his experience has been the aspiration of blood or infected matter during or following operations on the nose and throat or the extraction of teeth. The next most common cause has been bronchopneumonia. Contrary to belief the diagnosis is difficult to make. A differential diagnosis must be made between lung abscess, bronchiectasis and a small encapsulated or interlobar empyema. A careful history, sputum examination, roentgen ray, and physical examination are absolutely necessary. The roentgen ray is probably the most important, because it not only makes the diagnosis, but also pretty definitely localizes the process. Having made the diagnosis what is the correct treatment? All chronic cases should be operated on, the acute cases also unless the patient is in such a desperate condition that surgery is contra-indicated. The operative technic depends on the operator. The two-stage operation is the safest procedure to use, although it is ofttimes very much more difficult to find the abscess at the second operation. Whittemore describes his technic. The complications to look for following operation are empyema and hemorrhage, but the mortality should not be unduly high if the abscess is well localized and the correct time for operation is chosen.

Late Hereditary Syphilis and the Chronic Abdominal Syndrome.—Castex-Del Valle (*Surg., Gynec. and Obst.*, 1920, xxxi, 161) say that hereditary syphilis is a very frequent cause, perhaps the most frequent, of membranous perienteritis and analogous conditions. Its pathogenesis is complex as several factors operate, which set down in chronological order are: defects of conformation in the intestinal walls because of the faulty endocrine function which presides over and governs their development. These malformations on the one hand and the abnormal function of the nervous system (sympathetic and autonomous) owing to endocrine deficiencies produce defects in the gastro-intestinal statics and dynamics; as a consequence of the latter we have intestinal stasis which brings on chronic inflammation of the colon. From the wall of the colon the inflammation spreads to the surrounding serous membrane, aggravating the existing congenital lesions. The primary cause of all this is hereditary syphilitic infection, generally in the form of a late manifestation. These cases should first be given mixed antisyphilitic treatment with mercury chiefly. The surgical treatment is not to be abandoned, but is to be restricted to cases in which definite indications confirmed by clinical and radiologic diagnoses point to mechanical alterations of importance (kinks, adhesions, etc.) or to coexisting inflammatory lesions of adjacent organs—ovaries, tubes, appendix, gall-bladder, duodenum and stomach. Surgical treatment should consist in separating the membranes and in molding and mobilizing the peritoneum, together with careful peritonization and removal of the adjacent affected organs.

Pseudomyxoma Peritonei.—Biggs (*Annals of Surgery*, 1920, lxxi, 619) feels that this condition has not received the proper recognition from American surgeons. Pseudomyxoma peritonei is the result of the rupture of a pseudomyxomatous cyst of the ovary or the appendix into the general peritoneal cavity. The ovarian origin is by far more frequent. The epithelial cells which are set free are implanted on the

peritoneum where they produce pseudomucin and tumor formation. Failure of the condition to result from rupture of a pseudomyxomatous cyst is explained by (1) the infrequency of rupture of the smaller loculi which contain cells that are active but firmly adherent to their basement membrane, and (2) thinning of the walls of the larger loculi, the cells at the point of rupture not becoming implanted easily. The symptomatology is that of increased intra-abdominal pressure. The operative findings depend upon the stage in the disease at which the operation is undertaken. Early invasion of the peritoneum is characterized by a pebbly appearance. The average age of Bigg's patients was over sixty years, this showing that the lesion is one of advanced years. In order to attempt a cure the original growth, and as much of the implanted material as possible, should be removed. Although histologically benign, the condition clinically may be malignant. If operated on early the patient may be cured and at any stage the operation may inhibit growth.

Sarcoma of the Stomach.—DOUGLAS (*Annals of Surgery*, 1920, lxxi, 628) reviews the subject of gastric sarcomata and reports three cases. One per cent. of gastric tumors are sarcoma. The average age of patients suffering from this condition is 41.6 years, while that of carcinoma is 61.2 years. The earliest form to develop is the lymphosarcoma. This and the round-cell type are the most common forms. Although they are liable to be infiltrating the round-celled type may form pedunculated intragastric tumors. The round-celled variety results more frequently in ulceration, but this is not as common as in gastric carcinomata. The spindle cell and myxosarcoma are liable to form large exogastric tumors. Statistics show that the most common site is the pylorus, but the pylorus is less often attacked by sarcoma than by carcinoma. The diagnosis cannot be made with certainty. The metastasis is less rapid than in carcinoma, so that the operative prognosis is better. A gastric tumor with *x*-ray findings in a patient below the cancer age, the absence of blood in the gastric contents and stools, free hydrochloric acid and an absence of cachexia plus an anemia, points toward a diagnosis of sarcoma. The author reviews 230 cases besides the three he reports.

A Case of Cancer of the Pancreas.—KOETLITZ (*Arch. Med., Belges*, April, 1920, p. 291) reports a case of carcinoma of the pancreas which before operation seemed to be a carcinoma of the stomach. Exploratory laparotomy was resorted to to establish a diagnosis. There had not been any jaundice or steatorrhea. The palpable tumor semed to be a part of the stomach and the pain seemed to point to that organ. The pain, however, was not related to the patient's meals and was worse at night. Laparotomy and later autopsy confirmed the diagnosis of adenocarcinoma of the head of the pancreas.

Clinical Consideration of Osteomyelitis.—OCHSNER and CRILE (*Surg. Gynec. and Obst.*, 1920, xxxi, 263) say that osteomyelitis practically always has its origin in the medullary tissue, although at times it may originate beneath the periosteum and also as Iyars says: "Frequently there are two foci, one subperiosteal and one in the medulla." Early

and concise diagnosis and immediate surgical treatment are of the greatest importance. The operation should invariably consist in splitting the periosteum for a distance of 2 to 5 cm. beyond the area of pain upon pressure in the bone in each direction. In extremely severe cases this should be the extent of the primary operation. In less severe cases ultimate healing can be hastened by carefully opening the medullary canal at the point previously located because of pain upon pressure. Care should be employed to prevent traumatizing the tissues by rough chiselling. Moist hot antiseptic dressings with fixation of the extremity and with the use of electric light treatment increases the comfort and facilitates healing. The shaft of a long bone should never be removed until a good involucrum is formed. In late cases or in secondary operations upon cases treated as above in the acute stage, every particle of dead tissue must be removed. At this operation some definite plan must be carried out to facilitate closing the defect. Skin grafting is of great value in many cases. Local foci of infection such as abscesses of tonsils or teeth or sinuses, should invariably be eliminated at once upon undertaking the treatment of patients suffering from osteomyelitis.

The Treatment with Radium of Cancer of the Bladder.—KELLY and LEWIS (*Surg., Gynec. and Obst.*, 1920, xxxi, 303) say that cystoscopy has entirely altered all former methods of diagnosis as well as treatment. Of the various causes of blood in the urine, a bladder tumor is the commonest. For three reasons radical excision cannot always be the method of choice; the operation may be impossible on account of the site and extension of the growth. The operation is formidable and dangerous, considerations of age and physical condition having weight, and again it is followed by recurrence with notable frequency. Beer's use of the high frequency current for benign papillomatous growths frequently yields brilliant results. In a large percentage of the cases the growth is on the trigonum, which also prohibits any attempt at removal. In radium we have an effective means of treating at least some of these malignant growths of the bladder. After the patient is cystoscoped and the bladder distended with air, the radium on the end of a sound is placed close against the tumor. As a rule the emanation equivalent of a gram of radium is used for three to ten or more minutes. Such treatments can be given from one to four times in a fortnight. As a rule the application of radium checks the bleeding promptly. The infiltrative type of bladder cancer can, in a woman, be cross-fired from the vagina. A third method of treating these growths is to implant a capillary glass tube containing emanation directly in the tumor. Usually 5 cm. or more of emanation is imbedded and permanently left in place.

The Effects of Radium Emanations upon Brain Tumors.—FRAZIER (*Surg., Gynec. and Obst.*, 1920, xxxi, 236) reports three interesting cerebral lesions treated with radium emanations. Frazier points out several ways in which malignant brain tumors differ from malignant tumors of other organs: (1) they do not metastasize; (2) they frequently grow very slowly; (3) distinguishing feature of brain tumors is that the cardinal symptoms, headache, vomiting, and visual disturbances are attributable often not to the presence of the tumor but to secondary

ventricular distention; and (4) the inaccessibility of the growth on one hand or the absence of localizing signs on the other. Radical brain operations are prohibitive in all tumors except those distinctly encapsulated. Because of these many reasons there is a field for some physical agency which will not only arrest the growth of the malignant lesion, but even lead to a process of retrogression. Frazier in coöperation with Pancoast has used radium in the treatment of 24 cases of brain tumors. He reports 3 cases where the evidence points to an arrest and in all probability a destruction of the tumor. One of these cases was a pontile angle tumor, 1 a cerebellar tumor and 1 a pituitary tumor. Frazier considers radium therapy of importance especially in the latter cases following a sellar decompression. Frazier and Pancoast advocate direct implantation in the growth when feasible.

The Jones Operation for the Ankylosis of Subdeltoid Bursitis.—BLANCHARD (*Jour. Orthoped. Surg.*, 1920, cii, 466) says that subdeltoid bursitis is one of the most common and at the same time most frequently unrecognized of shoulder-joint injuries. The diagnosis is difficult in the first month. Blanchard reports a typical case with cure. The patient was anesthetized and held on an operating table so that the scapula rested securely upon the table. The assistant's fist was placed in the axilla so as to prevent a dislocation of the head of the humerus. The arm was moved firmly into abduction and rotated inward and outward and then pushed backward to its normal limit. Then the arm was given forcibly its full radius of movement. The breaking of the adhesions sounded like the fracturing of bones. Two days later the patient had normal function. The breaking up of the adhesions should not be done in a half-hearted way. This method is to be used only when the painful fixation is due a sterile deposit of lime salts.

Recklinghausen's Disease with Surgical Complications.—CALDWELL (*Surg., Gynec. and Obst.*, 1920, xxxi, 242) reports two cases of this disease. The author includes fibroma molluscum, neurofibroma, and plexiform neuroma under this title. The conditions he thinks may be due to an endocrine disturbance. Von Recklinghausen's disease should be regarded as a local manifestation of a general or constitutional vice. These patients are often of a low mentality and are often freakish. Besides the tumors of the skin a pigmentation suggestive of Addison's disease may be present. Psychoses are present in a number of cases. Tumors of the peripheral nerves and less frequently of the central nervous system are found. Skeletal changes and muscular distrophies are common. Tuberculosis is not an infrequent complication. There is a tendency for the cases to belong to the family type. Sarcomatous degeneration of the myxosarcomatous may occur in the neurofibromata. Neurovascular changes may occur. Neurofibromata are the most conspicuous of the lesions needing surgical interference. They are multiple and are disseminated over various peripheral nerves. The plexiform neuromata are less common and may be found in the central nervous system. Pain and interference of function may also warrant surgical interference.

PEDIATRICS

UNDER THE CHARGE OF

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Foreign Bodies in the Air and Food Passages.—GRAHAM (*Am. Jour. Dis. Children*, February, 1920) thinks that it is a reasonable conclusion that foreign bodies in the food and air passages are much more common than is generally believed. The statistics show that about 66 per cent. of the cases occur in children. The period of latency which follows the violent dyspnea and choking attack, and later the gra lual onset and chronic character of the symptoms, might lead one to suspect the presence of a foreign body. These are certainly often overlooked. The symptoms vary greatly. The peanut kernel immediately sets up a severe laryngitis, tracheitis and bronchitis. In the peanut cases the older child may survive the acute symptoms, but nearly always develops pneumonia. Metal objects may remain in the lung for a long while and do but little harm. It must be remembered that some foreign bodies do not cast a shadow on the plate. The location of such a body may often be diagnosed by allowing the patient to swallow a capsule filled with bismuth. The roentgen ray will show the bismuth-filled capsule held in position in the esophagus by the foreign body. Patients should not be allowed to cough in the hope of expelling the foreign body. This rarely happens. The physical signs and symptoms vary according to the composition, form, shape and size of the foreign body. Suspicion of a foreign body should be aroused by the following: An unexplained leukocytosis, localized symptoms in one lung that do not clear up under treatment, no tubercle bacilli in the sputum and a gradua failure in strength and weight. Bronchoscopy should be performed as soon as possible. There is no contra-indication except extreme weakness in the patient. In this case time should be allowed for the patient to react. In children no anesthetic is necessary. Roentgen ray should always be used. The asthmatoid wheeze when present is a sign of the greatest importance.

The Effects of Deficient Dietaries on Monkeys.—MCCARRISON (*British Med. Jour.*, February, 1920) records experiments made on monkeys. Ten were fed on autoclaved rice and four on autoclaved rice plus butter. Twelve monkeys fed on rice, banana, monkey nuts, milk, onions and bread served as controls. The rice was autoclaved at a temperatue of 130° C. for an hour and a half. An exclusive diet of rice so autoclaved may be considered to be wholly deprived of accessory food factors of all three classes, that is to say, that while excessively rich in starch it is deficient in fats, proteins and salts. A dietary of autoclaved rice plus butter is lacking in accessory food factors of the "B" and "C" classes, while it is ill-balanced with respect to proteins, carbohydrates and salts. The results of these experiments confirm those previously recorded by this observer in the case

of pigeons fed on similar food. They may be regarded as applicable in kind if not in degree to human beings subsisting on food similar in composition to that on which the monkeys were fed. Monkeys fed exclusively on autoclaved rice lost weight at the average rate of 18 grams a day. Those fed on autoclaved rice plus butter lost weight twice as rapidly or at the rate of 37.5 grams a day. As the animals were not weighed daily but only at the commencement and the finish of the experiments the averages given were approximate. It is probable that the loss of weight was much more rapid at the close than at the beginning of the experiment. The monkeys which received butter died much more rapidly than those which received none; the former in the average of fifteen days; the later in an average of twenty-three and four-tenths days. The sex of the animals appeared to have influenced the results to some extent, but the figures are too small to justify a definite conclusion. Dietaries which are deficient in vitamines and in protein, and at the same time are excessively rich in starch or in fat or in both, are potent sources of disease and especially of gastro-intestinal disease. An excess of fat in association with a deficiency of "B" vitamine and protein and superabundance of starch is especially harmful to the organism. Certain dietetic conditions greatly favor the entrance into the blood and tissues of bacteria. This is especially the case when deficiency of vitamines and protein is associated with an excessive intake of starch. Since life cannot be maintained in the monkey on a dietary almost wholly devoid of "B" vitamines, it would seem that complete absence of this vitamine from the food is of less practical importance from the standpoint of disease production in human beings than its subminimal supply. Complete deprivation of "B" vitamine, especially if there is also imperfect balance in other essential food requisites, leads to rapid dissolution and death; the subminimal supply of this vitamine will lead to slow dissolution and death. The results given in this paper may explain the great mass of ill-defined gastro-intestinal disorders and vague ill health which forms such a high proportion of the human ailments of the day.

The Etiology of Arthritis Deformans in Children.—Byfield (*Am. Jour. Dis. Children*, February, 1920) reports ten cases. It was interesting to note that there was a uniformity in the constitutional signs and symptoms, the chief ones being emaciation of varying degree, anorexia and irregularity of temperature rising to 100° to 103°. A leukocytosis of from 11,000 to 25,000 was present. On admission to the hospital enlargement of the spleen was never found. A positive tuberculin test was seen in only one case. A rheumatic history was obtained in a few cases, but in only one instance was more than one member of the family similarly affected. The teeth were examined in every case and in only one were they found to be diseased. Blood cultures were taken in two cases and were negative. The disease tended to have its onset in the larger joints, usually the knee or the ankle, while the bones and articulations of the wrist were affected later. In two cases the condition remained monarticular for a long period of time, suggesting tuberculosis of the joint. These cases resemble the group which are commonly referred to as rheumatoid

arthritis. One case gave a positive Mantoux reaction and a diagnosis of Poncet's disease might have been considered. After two operations of the sinuses, which was followed by a subsidence of the joint swelling and pain, the inference was that there was arthritis deformans in an individual suffering with tuberculosis. The chief cause of this condition is from chronic infection in the tonsils and adenoids and accessory sinuses of the nose. In children under three years of age the portal of infection seems to be limited to the tonsils and adenoids. After this time removal of the tonsils and adenoids is not effectual in arresting the progress of the disease. A sinus infection should be suspected as an etiological factor if, after the tonsils and adenoids are removed, there remains elevation of temperature, leukocytosis, poor appetite, together with a slowness of the joints to become less painful and swollen. Relapse and exacerbations are definite indication of the need of nasal treatment. From the case mentioned previously he thinks that Poncet's disease is nothing more than arthritis deformans in an individual with tuberculosis. Although supportive and orthopedic measures are helpful, surgical treatment of the nasal sinuses is to be considered as the most important therapeutic agent. As for the prognosis it is good as far as arrest of the disease is concerned, but the deformity and functional disability may persist for a considerable period.

Pneumonia in Infancy and Childhood without Physical Signs.—FREEMAN (*Arch. Ped.*, January, 1920) in this paper reports three cases in which the lesion was present, but gave no physical signs. Such cases, he says, have been previously called central pneumonias. He is strongly of the opinion that in children a positive diagnosis of pneumonia can be made without the presence of physical signs in the chest when there are several of the following symptoms present: Fever, overactivity of the alæ nasi, a pneumonic type of respiration with a pause at the end of inspiration accompanied by expiratory grunt, a relationship between respiration and pulse approximating 1 to 3, and particularly if there is the added sign of rigidity of the upper extremities, an effort on the part of the child to protect a sore chest. Since the adoption of the routine use of the roentgen ray in hospital cases, pneumonia has been found when no physical signs of its existence have been found, and even after its demonstration by the roentgen ray and the determination of the pneumonia subsequent physical examinations have proved entirely negative. It seems important, therefore, to demonstrate, as far as possible the existence of such cases without physical signs, in view of the fact that at present it is often difficult and impossible to obtain satisfactory roentgenograms of sick children in private homes. There is an urgent need for a roentgen apparatus which can be used in private houses without the great expense now involved in such work.

Auriculoventricular Heart Block in Children.—EYSTER and MIDDLETON (*Am. Jour. Dis. Children*, February 1920) report a case of partial auriculoventricular dissociation developing in a child aged two years, apparently associated with an acute nasal and throat infection.

This child had been under observation for two years. The cardiac condition is that of a well-compensated mitral lesion, associated with a 2 to 1 auriculoventricular block, with a ventricular rate between 50 and 60. The child has developed normally and at the time of the report was in apparent good health and is normally active. A search of the literature has revealed twenty reported cases of heart block in children. Nearly all of these were definitely or probably of congenital origin or occurred during the course of a severe and usually fatal diphtheria. This case is regarded as of special interest, because of its origin and the relatively mild clinical disturbance produced by the condition.

Scorbutic Beading of Ribs.—HESS and UNGRE (*Am. Jour. Dis. Children*, May, 1920) remind us that for many years beading of the ribs has been regarded as a sign characteristic of rickets and as really pathognomonic. The authors noted that in a study of rickets beading varied not only in degree but also in kind. Beading of the ribs may be due to scurvy. The difficulty of concluding in a case of scurvy that beading is scorbutic is that possibly rickets may be present as a complication. The writers have had exceptional opportunity to see cases in which beading developed in spite of the fact that infants had been receiving adequate amounts of cod-liver oil for long periods. In three cases not only marked beading, but enlargement of the epiphyses as well, developed, although the babies had been receiving cod-liver oil for a period of four months or more. Further proof of the scorbutic character of these lesions was the fact that both the beading and the enlarged epiphyses were reduced markedly in size within six weeks after giving orange-juice. Canned tomato is also recommended as an antiscorbutic. Scorbutic beading occurs in animals. This has been noted by many who have produced experimental scurvy. Beading also occurs in beriberi and pellagra. It is evident that the fact that beading of the ribs may be likewise of scorbutic origin has clinical and diagnostic significance. Unless it is certain that a baby has received an adequate amount of antiscorbutic food we are not justified in considering the enlargement of the costochondral articulations as of rachitic origin. The rosary may be of two-fold nature, as these two nutritional disorders frequently coexist. This does not imply that the same defect in diet produced both, for it is known that a small quantity of fruit juices will prevent scurvy but not rickets, and, on the other hand, that cod-liver oil will generally prevent the development of rickets but has no prophylactic value for scurvy.

The Antineuritic and Growth Stimulating Properties of Orange-juice.—BYFIELD, DANIELS and LOUGHLIN (*Am. Jour. Dis. Children*, May, 1920) undertake to show that orange-juice has properties of benefit to artificially-fed children other than its antiscorbutic action. It is generally conceded to be a mild cathartic, although this has been denied by Gerstenberger, who contends that its action is constipating. The diuretic action has been noted by Gerstenberger and also by Hess. It has been used in marasmus by Gladstone combined with apple-juice. Oranges and fruits in general, although valuable antiscorbutics, have not been regarded as sources of the antineuritic vitamin. The results obtained in this study by the addition of orange-juice to or the

omission of orange-juice from the diet of babies was uniform and constant. Under the conditions, maintained growth, as evidenced by weight curves, was in all cases stimulated when orange-juice was administered. On the other hand orange-juice from which the antineuritic vitamin had been removed was without influence. The fact that the changes produced were usually apparent within a day made the results more significant. That other constituents of orange-juice, as for example, the carbohydrate, played no part in the results was shown in one case. Dietary increases, both during and after an orange-juice period, were without marked effect. Furthermore, the addition of 3 gm. of sugar was also without an appreciable effect. In some cases the gains were less marked than in others, the greatest gains having been made in those babies receiving the most food, based on their theoretical weight. If the caloric intake per kilogram fell to ninety or therabouts there was less stimulation. Up to the present studies dealing with the influence of the antineuritic vitamin on growth have not shown whether the weight increases were due to the stimulation of appetite, and thus an increased ingestion of food, or to the direct influence of the antineuritic element upon metabolism. While this study does not attempt to solve this problem the observations were made with this point in view. In no case was a loss of appetite apparent, the same amount of food being taken during the entire course of the experiment. In animal experiments the conditions are quite different and the appetite is greatly diminished, so that when antineuritic vitamin is added the effect upon the appetite is marked. It appears to these observers that the appetite factor plays only a minor role in the stimulating effect of the water-soluble vitamin on growth provided a nearly adequate amount is being given. The question as to whether the antiscorbutic vitamin has growth-stimulating properties has not been the subject of expensive experimentation. It has been reported that receiving it showed better weight gains. The observations of this study fail to bear this out. There is little information regarding the coexistence and quantitative relationship in foods of the two water-soluble vitamins, the antineuritic and the antiscorbutic. Orange-juice has been shown to contain both in appreciable amounts. Tomato, banana, cabbage, potato and turnip also contain both in demonstrable amounts.

The Intestine in Small Children.—Robbin (*Am. Jour. Dis. Children*, May, 1920) measured the intestines and body length in 185 children at postmortem. He found that the length of the large intestine was between 80 and 130 per cent. of the length of the body in 91.3 per cent. of the cases. The small intestines were 500 to 900 per cent. of the length of the body in 79.9 per cent. of the cases. An unusually long large intestine was not accompanied by an unusually long small intestine, and an unusually short large intestine was not accompanied by an unusually short small intestine. There was no association of an unusually short or long small intestine with the clinical condition causing death. There was no correlation between an unusually short or long large intestine and the clinical cause of death. An unusually long large intestine might be a potential factor in the causation of chronic intestinal indigestion or chronic constipation. The body grows somewhat more rapidly in length during early life than either the small or the large intestine.

OBSTETRICS

UNDER THE CHARGE OF

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Gangrenous Appendicitis Coincident with Labor.—GRATTIN (*Surg. Gynec. and Obst.*, November, 1919) publishes an interesting and extraordinary case: The patient was a primipara, who, upon examination, had no abnormal physical conditions. By reckoning the child was expected at the latter part of the month of October. July 15 of the same year her physician was summoned to relieve epigastric distress, which was increasing. There was slight nausea, but no pain. Alkalies and carminatives failed. Gastric lavage and an enema were given, which greatly improved the patient's feelings for two days. There were no labor pains and no abdominal pain. On the following day deep pressure revealed abdominal tenderness in the right lower portion. A lesser degree of tenderness could be found in the left iliac region. The patient had symptoms of beginning labor. Appendicitis was diagnosticated and an operation was performed. The pregnant uterus was high in the abdomen and could best be reached by an oblique incision four inches in length, and necessitating a high and extremely lateral incision. When the peritoneum was opened several ounces of a slightly turbid fluid escaped, and this fluid seemed to be of general distribution. The uterus was held to one side while the operator explored the gall-bladder region, finding a tense, fluctuating and sausage-shaped mass near the cecum. This was very carefully delivered through an abdominal incision and was found to be a completely gangrenous appendix, distended with fluid, but not perforated. The proximal half-inch was still firm enough to ligate, and after being crushed with the clamp the pedicle was tied with catgut. The appendix was removed without accident. Drainage was employed after the operation and very careful closure of the abdomen was practised. The appendix was readily removed and the abdomen closed without drainage. On examining the appendix it was fusiform in shape, dull on the peritoneal surface and contained about two drams of foul, sanious pus. The appendix was in a stage of gangrene, but fortunately a rupture had not yet occurred. The tissues had been under a very great strain. When labor developed the patient was kept under the influence of morphin during the early part. In the second stage she was delivered under partial narcosis by forceps without difficulty. There was very little laceration. The placenta came away normally, but the child suffered from apnea, requiring artificial respiration and the use of the lung motor. The cyanosis diminished and respiration finally became established. This occurred two and a half hours after the birth of the child. Respiratory paralysis, however, developed, with attacks of apnea, and the child died. At autopsy he examined the baby by catheter, examining the urine for traces of morphin, thinking that perhaps the doses of morphin administered to the mother before and after the removal of the appendix might have had an influence; the

forceps could be eliminated as a cause of the fatal death and the child evidently perished from toxemia. The mother apparently did well, but then developed an irregular pulse, for which digitalis was given intravenously, and the drip method was kept in constant operation. A condition of shock developed and very free stimulation was necessary to cause the patient to rally. The intravenous injection of medicine seemed to be of direct avail. The patient's toxic condition continued, with attacks of heart failure and a gradual increase in the secretion of urine. There was considerable fever without peritonitis. On the sixteenth day after operation, after the patient had been taken home from the hospital, she developed a temperature of 104°. This continued for two days, without pain. Vaginal examination revealed nothing, and there was no pain in the wound. On the twenty-second day pain was described along the crest of the ilium to the outer side of the wound. Under anesthesia the finger was gradually introduced by stretching the tissues at the drainage-point of the wound and the index finger was inserted. There was a big sanguinous exudate to the outer side of the wound. The peritoneum seemed firm and healed and the exudate was broken up with the fingers and a rubber tube inserted. The temperature dropped and remained normal for three days. The wound gradually healed, and when the patient was discharged the pelvic conditions were found to be normal, without residual pelvic exudate. The salient points in this case are the simultaneous occurrence of labor pains, with abdominal symptoms ending in appendicitis. The appendix was totally gangrenous and greatly distended, and there was a beginning peritonitis. The baby was at full term, but died seven hours after delivery, with attacks of apnea, and finally failure in the action of the heart. The mother narrowly escaped death from postoperative toxemia, the functions of the kidney and heart being very difficult to maintain. Jaundice followed this and showed the effect of the toxemia upon the liver. The patient finally made a complete recovery. The reviewer had an experience somewhat resembling the above case which illustrates how insidious is the course of appendicitis in parturient women: A multipara, giving a history of good, general health, became toxic during her second pregnancy, and labor was induced successfully. Mother and child did well and the mother nursed the infant and went from the hospital to her home. During the week following she was taken with high fever and indefinite pain in the right lower abdomen. Purgation relieved her symptoms and her condition seemed practically normal. There was tenderness on deep pressure, but very moderate fever and general improvement. A leukocytosis of 20,000 was found, and in spite of the patient's comfortable, general condition operation was considered imperative. Pelvic examination revealed nothing. At operation a very large gangrenous appendix was found, the inflammation having extended to the right broad ligament to such an extent that when the right Fallopian tube was brought up it separated from its origin and attachments in the hands of the operator. The appendix was removed and found to be gangrenous. Although it had not, so far as could be seen, perforated, the entire right lower abdomen had become infected. Very free drainage was employed by using two large rubber tubes with gauze packing around them. This was gradually removed, the patient ultimately making a good recovery. The most careful search through the

history of the patient failed to reveal evidence of a distinct attack of appendicitis at any time during her life. During her pregnancy she had been in very good, general health until the development of toxemia just before delivery.

Myomectomy during Pregnancy.—FARMAR (*Med. Jour. Australia*, May 10, 1919) records the case of a patient three months pregnant who suffered greatly from intense pain in the right iliac region. After incision the mass was shelled out, leaving a fairly deep crater, but not exposing the uterine cavity. The muscular walls of the cavity were closed by catgut mattress sutures and then the peritoneal cuff was inverted and closed by a continuous Lembert suture of cotton thread. The abdominal wall was brought together in the usual manner. The tumor removed weighed 425 grams. The patient made a perfect recovery and subsequently gave birth to a healthy boy.

The Legal Aspect of Operating on a Pregnant Woman for Supposed Tumor.—In the *Journal of the American Medical Association*, July 19, 1919, is quoted a decision of the District Court of Appeal of California, First District, Division 1, affirming a judgment against a physician for having, as was alleged, negligently and without occasion therefor, performed a surgical operation on a married woman, aged twenty-two years. The patient alleged in her complaint that the physician informed her that she had a tumor in the Fallopian tube and that he operated upon her for its removal. As a matter of fact she was pregnant and five months later gave birth to a child weighing nine and a half pounds. The patient testified that when she first called the physician she told him that she had been having severe pains in her back and head and also in the pelvic region, was having scanty menstruation for almost a day each month and informed him that another physician had said he thought she was pregnant five or six weeks. The patient also testified that after the operation she heard the physician say that he had made a mistake and that she had heard others make the same statement. In the defence the physician testified that in addition to the symptoms which the patient described she told him that she had been having hemorrhages between menstrual periods and had some dizziness, that she did not suspect herself to be pregnant and that her condition then was nothing like what it had been with her first child. That so far as the history of the case went she might have had a fibroid tumor. That her condition was serious and required an operation and that an incision of about two and a half inches was made, when the diagnosis of normal pregnancy was established and the wound was closed and the abdomen dressed. Against the physician it was urged that he should have kept the patient under observation perhaps for six weeks before operating, when a correct diagnosis could have been made. As regards the necessity for operation experts testified that immediate operation was indicated only when there was hemorrhage between regular periods and that otherwise the patient should have been kept under observation until a diagnosis could plainly be made. The District Court held that if the jury in the first trial believed, as apparently it did, the testimony of the patient as to what she told the doctor relating to the history of the case then the operation was unnecessary and the original verdict

against the physician should be allowed to stand. As the patient closed her case without introducing expert evidence the counsel for the physician moved for a non-suit, arguing that the mere statement by the physician to the patient and her mother that he had made a mistake in diagnosis was not sufficient to establish negligence in the absence of testimony that such incorrect diagnosis was arrived at by reason of negligence. Assuming this to be true it was sufficient that evidence was introduced later in the case which tended to supply this defect and it did not appear that this evidence injured the physician.

Full Term Ectopic Pregnancy.—Rolls (*Am. Jour. Obst.*, July, 1919) reports the case of a young primipara in the twenty-second week of gestation. At six weeks a catheter or sound had been introduced, and this was followed after several days by considerable bleeding and the discharge of clots. An abortion was thought to have occurred, but four days before coming under observation the patient's abdomen suddenly became larger. When examined the uterus was symmetrically enlarged and the fundus just above the umbilicus and the placental bruit could be distinctly made out. The natural diagnosis seemed to be an intra-uterine pregnancy further advanced than the history indicated. Five months later, and very near full term, the patient was again seen and found to be in good condition. About a week previously she had pain over the gall-bladder, with nausea, vomiting and constipation and the vomiting of small quantities of highly colored urine. The patient was slightly jaundiced, and this was unrelieved by catharsis, diet and colonic irrigation. The temperature was 101°, pulse 144 (weak and irregular), respiration 30 and difficult. Palpation revealed a firm mass extending from the upper left quadrant of the abdomen to the umbilicus, and this gradually became an indefinite cystic mass. There was well-marked dulness on percussion in the flanks. Just below the umbilicus, in the left side, a fetal heart was heard and below this a placental sound. On vaginal examination the cervix was displaced to the left and the finger could be passed only to the internal os. There was a cystic mass behind the cervix, with an indefinite firmer mass above and to the right and below the level of the internal os. There seemed to be a small fetal part which could be made out. A provisional diagnosis of full term pregnancy with toxemia, complicated by incomplete rupture of the uterus or twisted pedicle ovarian cyst. Examination at the fifth month was thought to rule out ectopic pregnancy. After being in the hospital about half a day the patient was considerably better. The fetal heart could not be heard nor were fetal movements obtained. Improvement continued, the blood showed 10,400 white cells and the patient was without pain. At consultation the opinion was advanced that probably full-term ectopic gestation was present. Six days after coming to the hospital abdominal section was done, and as there had been considerable vaginal bleeding the vagina was packed without introducing the sound into the uterus. Bloody serum escaped and the fetus was found, showing distinctly through the thin sac. This was adherent to the omentum, large intestine and parietal peritoneum, while its pedicle was in the region of the left broad ligament. The sac was opened and a full-term child and amniotic liquid were removed. When the adhesions were broken up the pedicle was at the side of the left tube and extended to the uterine horn, but did not involve the fundus of the uterus. By

clamping the tissues the placental membranes were removed, with small loss of blood. The uterus was about the size of a four months' pregnancy and had been carried backward, upward and to the left. The pedicle was secured with ligatures and sutures, portions of membrane were removed from the omentum, intestines and peritoneum, with very slight hemorrhage. The abdomen was closed without drainage, the patient making an uninterrupted recovery. The child was macerated, weighing nine and a quarter pounds. It was mature, with no deformity. The placenta had two portions, and on the embryonal side a very short, thick pedicle, which when examined by the microscope showed edematous smooth muscle. Autopsy on the child revealed a transudate of serum in the abdominal, pleural and pericardial cavities.

Pregnancy Complicated by Volvulus of the Sigmoid Flexure, with Intestinal Obstruction.—DONALDSON (*British Med. Jour.*, December 13, 1919) describes the case of a primipara, aged thirty-six years, thirty-seven weeks advanced in pregnancy. The patient had always suffered from constipation, but had been fairly well during pregnancy. Recently she had slipped in the street, recovering herself without actual falling, and had after this a pain in the side which she though came from a muscular strain. Three days later, as the bowels had not acted, she sought medical help. When the physician saw her she had intermittent pain, and he examined her to see if labor had begun. There was no evidence of this, and she was treated with laxatives and enemata and without the passage of flatus or fecal matter. Two days later she was sent to St. Bartholomew's Hospital. On admission pulse and temperature were normal and there was no vomiting, and the patient did not look badly. Pregnancy was present, but in addition over half of the abdomen was very much distended. There was general tenderness and the upper part of the uterus was covered by distended bowel and the uterus pushed to the left. The position of the fetus was normal and there was no obstruction of the pelvis. At operation free fluid was found in the abdomen, and on examination this was sterile. As the uterus was at term it was pressing upon the intestines to such an extent that the operator performed Cesarean section and after this had been done the uterus could be kept out of the abdomen and the intestines examined. The pelvic colon, transverse colon, with a large loop of small intestine, were greatly distended. There was a volvulus of the sigmoid flexure, involving also a large loop of small intestines. The volvulus had one and a half twists, the bowel was untwisted and considerable time was given to emptying the colon through a rectal tube. As the patient's condition was critical the abdomen was closed without anchoring the colon to the abdominal wall. The patient and her child made an uninterrupted recovery.

Labor; Shoulder Presentations.—IPPOLITO (*Gazz. d. Osp.*, 1919, xl, 137) quotes the statistics of various countries regarding the frequency of shoulder presentation: Italy, 1.40 per cent.; Austria, 0.71 per cent.; France, 0.66 per cent.; Belgium, 0.59 per cent.; Germany, 0.58 per cent.; England, 0.36 per cent.; United States of America, 0.35 per cent. The writer has practised for twenty years in Sicily and in 10,000 labors; he has seen 150 cases of shoulder presentation. Among his pateints contracted and deformed pelves are not uncommon.

GYNECOLOGY

UNDER THE CHARGE OF

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Radium Treatment of Carcinoma of the Uterus.—From April, 1914, to October, 1919, 165 cases of carcinoma of the uterus were subjected to radium treatment by SCHMITZ (*Wisconsin Med. Jour.*, 120, xix, 157), and for the purpose of study of the clinical value of radium therapy, he has divided the cases into five groups: Group 1. Cases which were clearly operable after a physical examination Group 2. Cases which were doubtfully operable: (*a*) cases subjected to surgery and ray therapy, and (*b*) cases subjected to ray therapy only. Group 3. Cases in which an operation was absolutely impossible: (*a*) cases subjected to abdominal hysterectomy and ray therapy; (*b*) cases subjected to vaginal cautery and ray therapy; (*c*) cases subjected only to ray therapy. Group 4. Cases so far advanced that all treatment was hopeless, which were subjected to ray therapy for purposes of palliation. Group 5. Cases that recurred after an abdominal panhysterectomy. A study of the results obtained demonstrates at once the importance of early diagnosis and treatment. We can hope for cure or improvement in cancer statistics only by instituting measures resulting in an earlier recognition and immediate proper treatment of these carcinomata. The clearly operable cases made a remarkable and favorable showing. There were two deaths in a total number of 12 cases treated. The living cases have gone from one to five years without any sign of recurrence. In Group 2, 20 cases were treated. Of these 13 were subjected to operative and ray therapy. Of these 7 are living while 6 either died or did not report. Of the 7 cases treated only with rays 5 are living and 2 died. It is impossible to state whether an operation should have been performed or not as the cases are too few and too recent to permit a conclusion. However, it appears to Schmitz that surgical eradication does not materially influence the results for the worse. It is not surprising that Group 3 presented the largest number of cases, namely 73. Of these 16 cases were subjected to hysterectomy either before ray therapy was begun or after a local healing was obtained with ray therapy. The results were disastrous. Only two patients have survived the ordeal. Twenty-one cases were subjected to an initial vaginal cautery before radium was applied. Three patients survive to date, while the average duration of life in those known dead is twelve months. On the other hand, 11 of the 37 patients treated only with radium therapy are well at the present writing. The duration of life of those that died in class (*a*) is nine months, in class (*b*) twelve months, and in class (*c*) twelve

months. In other words the patients in the latter class had a better chance all around than those in the former class. We must conclude that if local healing is obtained, the tumor is arrested in growth and the infiltration of the parametria subsides, we should not subject the patient to an unnecessary operation. This conclusion of Schmitz is in entire harmony with our own belief which is based upon our experience with this class of cases as seen in our service in the University of Pennsylvania Hospital and which dictum we have been emphasizing for several years. Group 4 demonstrates one fact. An advanced cancer patient should be treated only with ray therapy to relieve the symptoms as this is all we can hope for, but even then little benefit is obtained for the efforts spent. The intensive intermittent plan of treatment cannot be carried out in this class of cases as the rapid generation of tissue invariably causes a severe auto-intoxication. A period of from four to eight days should intervene between applications, that is until the reaction has subsided. Group 5 shows a few brilliant therapeutic results. Recurrent carcinomata are very refractory to radium treatment. Comparing this group with groups 1 and 2, Schmitz deduces that a combination of surgical treatment and ray therapy shows such favorable results that surgical eradication of carcinomata must always be combined with an intensive ray treatment. If we procrastinate and postpone the latter until recurrences appear, and they do appear in about 75 per cent. of the cases within the first two years following the operation, then ray treatment also cannot improve the outlook in the majority of cases. It is his opinion that the sooner after operation the recurrence takes place the better the palliation from ray therapy.

Treatment of Calculi Impacted in Lower Ureter.—Many surgeons still appear to be under the delusion that directly a shadow of a stone in the lower ureter has been shown by roentgen-ray examination, they should immediately cut down and try to remove the stone. Nothing is more fallacious than this idea, states KIDD (*British Med. Jour.*, 1920, July 31, p. 160), which has led to many disasters. Experimental work on animals to determine how long a stone can lie in the ureter before damaging the corresponding kidney irreparably suggests that six months to a year is the longest time during which a stone ought to be allowed to obstruct the ureter. But from clinical evidence Kidd is convinced that such experimental work does not reveal the whole truth. In the first place, stones rarely block the ureter completely, so that natural conditions differ from many of the experimental conditions. In the second place, clinical evidence suggests that the kidney may recover sufficiently to do much useful work, even if the ureter has been partially blocked for many years by a stone. Provided then, that there are no imperative indications for operative interference, Kidd believes that it is advisable to give the patient one to two years in which to pass a ureteric stone naturally, aiding Nature by minor cystoscopic manipulations. The methods in use today for coaxing a stone down the ureter are: (1) Injection of sterile oil through a ureteral catheter around the stone, which may induce it to pass in a few days. (2) Injection of 5 c.c. of a 4 per cent. solution of papaverin sulphate locally into the ureter through a catheter. This alkaloid causes direct relaxation of unstriped muscle fiber, relaxing the ureteric muscle in the region of the

stone and has been successful in causing stones to pass. (3) Incision of the superior wall of the mouth of the ureter by means of the operating cystoscope and the special Lewis scissors, starting from the mouth of the ureter and cutting through the bladder wall for at least three-quarters of an inch. Following this, the ureter may be dilated and possibly the stone can be grasped and extracted. The slit in the ureteral mouth heals without stricture formation. Although Kidd has found it necessary to operate upon twenty-eight patients suffering from stone in the lower ureter during the past ten years and has only lost one case, nevertheless he wisely counsels reasonable delay in resorting to surgery and the employment of cystoscopic methods during such delay, if the best interests of the patient are to be served.

Radium in Benign Type of Bleeding.—Curtis (*Wisconsin Med. Jour.*, 1920, xix, 172) briefly summarizes his experience with radium therapy in bleeding from the uterus due to non-malignant conditions. There were 62 fibroid tumor cases which were subjected to the ray therapy. These were selected cases because the tumors were of moderate size and nearly all of the cases were treated for hemorrhage. Myomectomy or hysterectomy has thus far been given preference in younger women, in tumors of large size, and in cases with other pelvic lesions. Except in a very few instances no attempt was made to avoid bringing on the menopause and the treatment consisted of curettage with the intra-uterine application of 50 mc. of radium for a period of twenty to twenty-four hours. The hemorrhage always stopped but the decrease in the size of the tumor has varied considerably. Subsequent hysterectomy has been resorted to a few times because of symptoms from preëxisting pressure or adhesions. The menopausal symptoms, which sometimes occasion much annoyance, have been controlled by fresh corpus luteum or ovarian residue, especially the latter. The hemorrhage has invariably been controlled in the 81 cases of myopathic bleeding of the menopause which were treated. Under the term "idiopathic hemorrhage," Curtis includes those patients, who, in the absence of gross pathological changes, suffer from excessive flow during the child-bearing period. Most of such cases are ascribable to physiological disturbance of, or pathological interference with the ovarian function. Many of these patients dread artificial menopause, and delicate management is required to preserve menstrual function. For example, in a given case menorrhagia may be due to psychic disturbances which produce chronic pelvic congestion. Treatment with radium decreases the menstrual flow to normal. Thereafter, if the cause of functional disturbance is removed amenorrhea may follow. Again, women in the upper thirties, particularly unmarried women, are prone to menorrhagia. Sometimes the bleeding is a precursor of the menopause and certain of the patients are not relieved with moderate doses of radium. Others are particularly susceptible and the menopause is unexpectedly ushered in. Still, again, small doses may have no appreciable effect. After two or three applications the flow may increase rather than diminish. Another treatment is given and the menopause follows. The increased flow was a warning of an impending menopause. Two patients with idiopathic hemorrhage may react quite differently. Equal applications may cause a return of normal menstruation in both

cases, but two years later one may have a return of menorrhagia while the other may go on to early menopause. Certain facts are helpful in the management of these cases: Organotherapy occasionally makes radium unnecessary. If radium is used an amount in excess of 1000 mc. may induce the menopause especially in women over thirty-eight years. Increased flow after treatment suggests a possible menopause as does also an increase in blood-pressure. From the standpoint of ultimate results it is preferable to give repeated small doses, *e. g.*, 300 mc., at intervals not more frequent than once in three months, without control observation of blood-pressure and subjective symptoms.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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Hemolytic Streptococci in the Throat in Certain Acute Infectious Diseases.—Otteraaen (*Jour. Infect. Dis.*, 1920, xxvi, 23) examined the mouths, noses and throats of three hundred patients, most of whom had either diphtheria or scarlet fever, to determine the prevalence of hemolytic streptococci. Surface inoculation of goat's blood-agar plates was employed, although a higher percentage of positive findings was encountered when the enrichment method was used. While all organisms produced complete hemolysis the surface colonies varied considerably as to size and intensity of hemolysis. According to Holman's classification most of the fifty strains tested were either S. pyogenes or anginosus. Animal inoculations and phagocytosis experiments indicated that the organisms isolated were not virulent. Of the 300 cases, 46.6 per cent. showed hemolytic streptococci on admission and some became positive after entrance, making a total of 60 per cent. In the patients with diphtheria, positive cultures were obtained in 10 per cent. from the nose and 4.6 per cent. from the mouth, whereas in the scarlet fever cases the nose cultures were positive in 20.8 per cent. and the mouth in 12.8 per cent. Only a small number of patients yielded positive cultures from all three sources, the mouth, nose and throat. Those with positive nasal cultures, as a rule, had negative throat findings, and *vice versa*. When hemolytic streptococci were present in the nose, they were often predominating, while in the mouth they were usually found in small numbers. Negative cases which later became positive frequently did so after being in contact with carriers.

The Fate of Streptococcus Hemolyticus in the Gastro-intestinal Canal.—Pathogenic streptococci, especially hemolytic streptococci, gain access to the gastro-intestinal canal from the throat and tonsils where they have been shown to occur in normal individuals as well as by the ingestion of certain foods, particularly infected milk. While the strong

bactericidal effect of gastric contents on bacteria in the stomach is recognized and while hemolytic streptococci occur in normal feces in relatively few instances, little is known of the specific action of the intestinal juice on the Streptococcus hemolyticus. In an effort to ascertain the action and fate of hemolytic streptococci in the alimentary canal, DAVIS (*Jour. Infect. Dis.*, 1920, xxvi, 171) introduced into the stomachs of three rabbits, by means of a catheter, 10 to 20 c.c. of one avirulent and two virulent strains of these organisms. Each type of organism was fed for ten days to each of the animals, during which time daily examinations of the feces were made. It was found that hemolytic streptococci did not occur normally in any appreciable number in the gastro-intestinal canal of rabbits. When introduced into the stomach of rabbits these bacteria may occasionally pass through the canal and appear in the feces. At the end of thirty-one days the animals were sacrificed and examination of the gastro-intestinal canal at various levels indicated that the hemolytic streptococci did not develop to any great extent in the intestines, not did they readily gain a permanent foothold there. From additional investigations it was observed that rabbits with generalized streptococcus infections in joints and blood showed none of these hemolytic streptococci in the intestinal contents; that the gastric juice of normal acidity from man and rabbits killed hemolytic streptococci in from two to five minutes, while gastric juice in achylia may not kill them in several hours; that hemolytic streptococci were not found in the normal human feces of 53 cases and that hemolytic streptococci, when mixed with normal human feces lived in the icebox for several days, whereas in the incubator they tended to die out rapidly.

Relation of the Portal Blood to Liver Maintenance.—ROUS and LARIMORE (*Jour. Exper. Med.*, 1920, xxxi, 609) carried out a series of observations upon the liver following upon the partial occlusion of the portal vein. Rabbits were used in the experiments. They found that it was quite easy to completely shut off a large part of the portal circulation, leaving, however, a sufficient distribution to the right posterior and caudate lobes to maintain adequate liver function. As soon as the one branch of the portal vein is ligated the involved lobes become smaller and dark in color. In the meantime the mass of portal blood is diverted to the remaining branch and the lobes supplied by it become swollen and of brighter color. Hypertrophy of the latter lobes begins within three days and by the end of twelve days has more than doubled in size. Subsequently it slowly increases and eventually reaches the size of the entire original liver. A process of atrophy continues in the ligated portion, the lobe gradually dwindling to a shrunken fibrous mass. The connective tissues of the stroma do not show response either of the nature of replacement fibrosis or of inflammation. By these experiments three-fourths of the liver may be reduced to a fibrous tag within two months. The bile which is secreted from the liver mass advancing in atrophy is almost colorless and deficient in bile salts. The authors suggest that the results of the experiment should aid in an understanding of certain chronic liver lesions. It is indicated that the portal blood bears a relation to the liver not only for its functional capacity but also more directly for its vital support.

The Mycelial and Other Microörganisms Associated with Human Actinomycosis.—COLEBROOK (*British Jour. Exper. Path.*, 1920, i, 197) gives a series of 27 cases of actinomycosis, 17 in the years 1911–14 and the remainder since the war period. These were all true types of Actinomyces bovis, all showing suppurative lesions with visible granules in the pus and 25 per cent. of these showing clubs at the periphery of the granules. For purposes both of diagnosis and culture, actual granules were obtained from the pus. He first deals with the mycelial organisms isolated and later with the associated bacteria. He classifies the first into groups *A*, *B* and *C*. Twenty-one strains came in group *A*. These strains were filamentous organisms, being slender branching and seldom straight for more than 20 or 30 microns. They were Gram-positive but not acid-fast and showed a strong preference for anaërobic growth. Cultures were obtained on ordinary nutrient agar or broth but grew better with 1 per cent. glucose. Their viability was slight (60° C. for one hour killing the cultures). He identified this strain with the Actinomyces bovis of Wolff and Israel. Group *B* included two strains. They were similar to *A* in their preference for anaërobiosis, slight viability and morphologic features. However, they grew poorly on glucose agar and no aërobic cultures were obtained. Group *C* included one strain. The mycelium was perhaps straighter but otherwise similar to *A*. Cultures gave a single aërobic colony. Subculture on glucose agar gave several large flat rosettes which grew deeply into the media. The three remaining cases were not sufficiently worked out to be grouped. The author opposed the idea that the ray fungus was derived from grasses and vegetation, inasmuch as it is an anaërobe. He is more inclined to believe that it is a frequent inhabitant of the alimentary tract and from there is carried into the tissues. Coarse agglutination with the serum of heavily infected persons occurs up to 1 in 500 to 4000 dilutions. Similar results were obtained in sera of rabbits inoculated with a vaccine of Actinomyces bovis. In 30 cases, the granules of which were examined, 24 showed an associated organism having the following characters: coccoid forms or bacilli; no capsules; non-motile; Gram-negative; star-like colonies that adhered to the tube in fluid cultures; grew aërobically or anaërobically; viability slight (52° C. for half-hour kills); pathogenicity for man was not determined but for animals doses 300 to 15,000 millions produced death. He identified this organism with the *B.* actinomycetum comitans described by Klinger while working in Zurich. The author advanced four hypotheses trying to solve the reason for the presence of these organisms in over 80 per cent. of his cases. None of these, however, seemed satisfactory to himself. Other organisms, such as streptococcus and staphylococcus, may be found in the cervicofacial and abdominal cases of actinomycosis.

The Pathological Histology of Tonsils Containing Hemolytic Streptococci.—KELLERT (*Jour. Med. Res.*, 1920, xli, 387) disparages the growing tendency to attribute the source of systemic infections to the tonsils, stating that, though these organs may often harbor pathogenic bacteria, it is by no means a corollary that these lymphoid masses are therefore the initiators of the general disease. He further notes that an abrasion must be present on the mucous surface of the tonsil to provide a portal of entry for the infecting material, and yet many

ulcerated tonsils have been removed from adults who have previously manifested no distant affections. It is noteworthy, also, that the investigator through his own work and that of others, notably, Smith and Brown, Smillie, Nichols and Bryan, and Tongs, has been led to conclude that streptococci carriers are as definite and menacing an entity as are those of typhoid, dysentery and diphtheria and to this list must also be added meningococci and pneumococci carriers. The work in the various army cantonments with epidemics of hemolytic streptococci infections strengthens this conclusion. The author examined the material bacteriologically only for hemolytic streptococci. Seventy pairs of tonsils were cultured and examined microscopically. Cultures were made from both the mouths and from the depths of the crypts near the capsules. It is of significance to note that the greatest numbers of hemolytic streptococci were grown from the cultures taken in the depths of the tonsils. The figures for the frequency of finding hemolytic streptococci in these seventy instances are not presented. Grossly, the tonsils varied considerably in size and shape and all those showing hemolytic streptococci presented a more or less constant microscopical picture. No abscesses were encountered. The capsules were generally thickened with the branching trabeculæ showing a correspondingly denser structure. Old blood pigment, muscle and mononuclear cells were seen in the fibrous capsule. The writer feels that no analogy can be safely drawn between the chronicity of infection and the density of the capsule. Ulcerations of the mucous surfaces of the crypts with a penetrating infiltration of polymorphonuclear leukocytes and mononuclear cells were observed. Bacteria were present to a greater or less degree in all the crypts. The lymphoid follicles were hyperplastic and less definite in outline than normally. Cartilage was found in the capsule of 10 per cent. of those positive for hemolytic streptococci, and in 25 per cent. of those not showing this organism. The investigator's views are summarized in a terse manner wherein he observes that infected and diseased tonsils are not infrequent in healthy adults and that the largest tonsils are not necessarily the most severely infected. Inflammatory changes indicative of infection may be found in nearly all tonsils. The conclusion is drawn that hemolytic streptococci may be saprophytic in the tonsil and that no distinctive pathologic lesion can be assigned to this organism in the tonsil.

Observations on Changes in Virulence of Hemolytic Streptococci with Special Reference to Immune Reactions.—NAKAYAMA (*Jour. Infect. Dis.*, 1920, xxvii, 270) observed the changes in virulence of hemolytic streptococci produced by animal passage, growth in artificial culture and certain other conditions, at the same time noting the reactions with immune serums of streptococcal strains of varying degrees of virulence. It was found that the virulence of a streptococcus rapidly decreased on artificial cultivation, particularly on blood agar. The amount of peptone in the medium apparently did not influence the virulence so much as the reaction, acid reaction maintaining virulence better than alkaline. The virulence persisted longer under anaërobic than aërobic conditions. An avirulent streptococcus increased in virulence for both rabbits and mice on passage through the rabbit. When also passed through mice, the virulence was further increased, particularly for mice and when a certain maximum of virulence had been reached no further increase

developed on further passage through the mice. When the maximum virulence for mice had been established passage through rabbits sometimes increased virulence for rabbits but decreased for mice. On the other hand, if virulence for mice was still increasing, passage through rabbits could increase the virulence for both rabbits and mice. By keeping streptococci in a collodion sac in the rabbit peritoneal cavity, it was found that virulence may be increased. In the agglutination reactions, cinnabar was employed to obviate the action of minor agglutinin and to prevent spontaneous agglutination of the streptococci. It was learned that the agglutinability of a streptococcus may change as the result of animal passage, the particular strain used for immunization being agglutinated more strongly than the related strains by the corresponding immune serum. The original non-virulent strain of streptococcus was agglutinated by all the immune sera. The same relation seemed to obtain with reference to opsonins and phagocytosis, as well as with respect to specific precipitation and conglutination, but no difference between the different strains by means of complement fixation could be made out. All the various strains were agglutinated in the same way by acid solution.

Noma in the Dog.—Fusiform bacilli and spirilla are so universally found in the morbid tissues of noma, Vincent's angina and other phagedenic processes that, in light of our present knowledge, most writers believe that we are justified in considering them as the possible if not the probable causative agents in these processes. PHILLIPS and BERRY (*Jour. Infect. Dis.*, 1920, xxvii, 136) report typical noma in a dog, a cocker spaniel, which developed after a mild attack of distemper. The lesion began on the right lower lip and extended to the ramus of the jaw and tissues of the neck. Prostration ensued after eight days, death occurring on the thirteenth day, when the moribund animal was killed after pneumonia developed. Daily smears from the lesions, stained by dilute carbol-fuchsin, showed that B. fusiformis and spirilla greatly predominated over a small number of micrococci and short bacilli. In the later stages of the disease, the fusiform bacilli tended to form involution forms which frequently resembled thick spirilla. Attempts to culture the organisms anaërobically on glucose horse serum agar were unsuccessful. Smears from the gums of normal dogs showed only a few fusiform bacilli and spirilla. The authors suggest that dogs be used in experimental noma and call attention to the possibility of contagion from dogs to man.

Studies in Epidemic (Lethargic) Encephalitis; Cultural Studies.—In previous communications, Strauss, Hirschfeld and Loewe have reported the findings of a filtrable virus in cases of epidemic encephalitis. Later, a filtrable organism obtained from the virus by special cultural methods, was described. LOEWE and STRAUSS (*Jour. Infect. Dis.*, 1920, xxvii, 250) have reviewed the previous work, supplementing additional studies. The organisms appeared to thrive best when the original Noguchi technic was followed, employing sterile kidney fragments and ascites fluid medium. The optimum solid medium was gelatinous in character, consisting of nutrient agar, ascitic fluid and kidney tissue. Cultures made on ordinary media and by Rosenow's technic have proved negative. A minute filtrable organism has been cultivated from

the brain, nasopharyngeal mucous membrane, nasopharyngeal washings, spinal fluid and blood of epidemic encephalitis cases, while control cultures of material from human patients suffering from or dead of conditions other than epidemic encephalitis were found to be uniformly negative. Under dark field illumination, the organisms were minute, globular, refractile, non-motile forms, occurring singly in diploform chains and clumps, the latter form predominating. Young cultures on fluid media were Gram-positive, while the older ones and those on solid media appeared to be Gram-negative. Tinctorially, the organism was of a basophilic nature. The same organism has been recovered from the brain and nasopharyngeal mucous membrane of animals which were inoculated with virus or culture and which succumbed to the experimental disease. The cultures thus recovered have produced the disease when injected into other animals and the organism has again been recovered. Positive animal inoculations have been obtained with the eleventh generation of this organism. Berkefeld and Mandler filtrates of brain material, nasopharyngeal mucous membrane and washings, spinal fluid and blood from cases of epidemic encephalitis have produced in rabbits and monkeys lesions typical of the disease. The virus has been passed through many series of animals and can be preserved for months in 50 per cent. glycerol. The authors suggest that their results indicate that epidemic encephalitis can be differentiated from epidemic poliomyelitis since rabbits are susceptible to the infectious material of the former and not to the latter, and monkeys are very susceptible to poliomyelitis and relatively refractory to epidemic encephalitis. Again, spinal fluid from poliomyelitis is innocuous to rabbits and monkeys, whereas spinal fluid from cases of epidemic encephalitis produces lesions typical of the disease in both these animals.

A Study of Streptococci Obtained from the Mouth in Cases of Chorea.—The triad of articular rheumatism, endocarditis and chorea and their frequent association with streptococcic tonsillitis have furnished problems for repeated investigation, and further since the streptococcus has been shown to be the organism most commonly isolated in the group, lends added interest to the study of the streptococci found in the mouths of chorea patients. Floyd (*Jour. Med. Res.*, 1920, xli, 467) details his findings in the study of the streptococci obtained from the mouths of 26 individuals clinically manifesting chorea. Previously Mayer and Cole were able to produce acute arthritis and endocarditis in animals by the intravenous injection of streptococci obtained from various sources but only Beattie reports symptoms suggestive of chorea following the intravenous injection of streptococci and these were not typical. Westphal, Wassermann and Malkoff, Apert, Richter and Poynton and Paine isolated a diplococcus from cases of chorea and the latter were able with their diplococcus to produce choreiform twitchings, arthritis and endocarditis in rabbits, The author is impressed by the infrequent positive findings from blood cultures in definite cases. In the present instance cultures were taken from about the teeth and from the crypts of tonsils in 26 cases of acute chorea and planted upon Loeffler's blood serum or blood agar. The streptococcus was readily isolated from all but 3 cases. Blood cultures were negative as were the cultures of cerebrospinal fluid. Pure cultures of the streptococci were introduced into the peritoneum of mice and if fatal to the animal within twelve to twenty

four hours, subcultures were taken from heart's blood and joints and rabbits were inoculated intravenously. From 1 to 6 inoculations were required to produce fatal results in different animals and when death ensued immediate autopsy was performed and subcultures of organisms obtained from definite lesions were perpetuated for possible later therapeutic use. In 4 cases definite vegetative endocarditis was developed in the rabbit and the infective organism in three of these was from tonsil while the fourth was from teeth. Eight animals manifested acute swelling of joints with definite crippling. The brain of the animals showed only engorgement of the pial vessels. Ten children with healthy throats were cultured as control cases and from only three of these were streptococci grown and not one of these was pathogenic for the mouse. An attempt was made to determine some method for therapeutic usage of the virulent organisms. However, in all attempts the results proved negligible. The author was able to prove satisfactorily that members of the streptococcus group may be isolated from the pathological lesions in endocarditis, articular rheumatism and chorea. He found also that the percentage of virulent streptococci about the teeth and in tonsils of chorea patients is much higher than in normal throats.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Possibilities of Using Mosquito Traps in Antimalaria Work.—METZ (*Public Health Reports*, 1920, xxxv, 1974) states that the control of malaria is rapidly becoming a rural problem as the expensive mode of eradication applicable to urban communities cannot be applied to country districts under present economic conditions. The writer noted that Anopheles were attracted by pigs and a pen was devised which served as a trap, allowing the mosquito to enter but not to emerge. It is suggested that a chemical agent might take the place of the pig and that the whole subject is worth full study.

Necessity of Low Temperatures for the Preservation of Vaccine Virus.—The Public Health Service (*Public Health Reports*, 1920, xxxv, 1762) publishes a warning against keeping vaccine virus under unfavorable temperature conditions. It is pointed out that the virus should be kept in contact with ice during the summer period and at a low temperature at all times. Special refrigerating devices are recom-

mended for shipment in hot weather. Vaccine virus should not be carried in the doctor's vest pocket. A few hour's summer heat may destroy the viability of the vaccine. The chief cause of negative takes during the summer season is failure to keep the virus cold.

Mosquitoes and Bats.—It appears according to HOWARD (*Public Health Reports*, 1920, xxxv, 1789) that the insect-devouring habits of bats are being employed to reduce the mosquito nuisance in some sections of this country. The warning is issued that this method of mosquito control is on a purely experimental basis and not to be depended on unless further controlled work shows the practicability of this method.

Soaps in Relation to Their Use for Hand-washing.—NORTON (*Jour. Am. Med. Assn.*, 1920, lxxv, 302) states that sterile hands are not obtained in the ordinary process of hand-washing. More bacteria were found to be removed by the ordinary toilet soaps than by the special soaps. In other words the cleansing properties of a soap are more important than its "germicidal" or "antiseptic" constituents. The soap solutions obtained in hand-washing are of no practical germicidal or antiseptic value. The soap left on the hands after washing has no germicidal action. In the whole process of hand-washing done in the usual manner the special so-called "germicidal" or "antiseptic" soaps exhibit none of these properties. Therefore, these terms are not proper to use in connection with soaps. Finally, since the hands may serve as a medium for the conveyance of bacteria in infectious diseases it is important to remove these bacteria; this may be done by the ordinary toilet soaps as effectively, if not more so, as by the special brands of so-called "antiseptic" or "germicidal" soaps.

The Value of Prophylaxis Against Venereal Diseases.—MOORE (*Jour. Am. Med. Assn.*, 1920, lxxv, 911) states that the low annual incidence rate of venereal disease during the war was due to several factors which have been discussed in recent communications. The various methods employed, however, would have accomplished less satisfactory results had it not been for the use of prophylactic measures. During 1918–19, as consultant urologist to the District of Paris, the writer was able to study the results of prophylaxis on a large scale. He states that Ashburn concludes that the measures employed in combating venereal disease were effective in this order: (1) Those that keep men chaste; (2) those that diminish the opportunities for sexual contact, especially efforts at the suppression of prostitution; (3) those that diminish the dangers of contact, especially venereal prophylaxis: (4) those that exact punishment. The method of prophylaxis used was as follows: Under no circumstances was a patient (even an officer) allowed to administer the treatment to himself; it must always be done by the attendant. If for any reason the attendant was unable to employ the treatment exactly as directed, he must state the reasons therefor and the deviation adopted on the prophylactic record. As a first step the patient was instructed to urinate. Then he was provided with a pint of warm water in a basin and a gauze wipe, with which he washed thoroughly, while the attendant

dropped liquid soap on the penis. An examination of the genitalia was made; if the patient had a discharge or a genital sore the fact was noted on the record and the patient instructed to report to the clinic; but this was as far as the attendant was allowed to go in making a diagnosis. He must continue the treatment as usual. The next morning, on receipt of the records at the clinic, all such records were separated from the others and the commanding officer of the patient's organization requested to have him report for examination at once. The next step was the injection of 1 dram of a 2 per cent. protargol solution (freshly made twice a week and kept in a closely stoppered bottle to avoid deterioration) into the urethra by the attendant. The patient then held the meatus firmly between the thumb and forefinger for five minutes, from time to time allowing a drop to escape from the meatus, so that all parts of the urethra were in contact with the solution. At the end of five minutes, the protargol was allowed to escape without pressure, so that a few drops remained. One-half dram of 33⅓ per cent. calomel ointment was next rubbed thoroughly by the patient, under the observation of the attendant, into all parts of the penis for five minutes, special attention being paid to the retracted prepuce, the frenum and the glans. Finally the penis was wrapped in toilet paper to protect the clothes and the patient instructed not to urinate for four or five hours. Throughout, the strictest precautions as regards sterility of syringes by boiling was maintained to prevent transfer of infection from one patient to another. So far as the district of Paris was concerned the use of the prophylaxis was the largest single factor in the prevention of venereal disease. With Ashburn's figures on the relation of exposure to disease as a basis for argument it is estimated that 2571 new cases of disease were prevented. The method of prophylaxis described is calculated to make the treatment more efficacious. The statistics presented show that prophylaxis is 99.6 per cent. efficient in the circumstances under which Moore employed it. Prophylaxis is probably equally efficacious against all three venereal diseases.

High Incidence of Typhoid in Small Epidemic.—LEAKE and MESSER (*Public Health Reports*, 1920, xxxv, 2197) observed an epidemic of typhoid fever due to an infection of a salad served at a banquet at which 49 among 90 diners developed the disease, making an incidence of 54 per cent. Many cases were atypical and a considerable number occurred among persons who had been vaccinated against typhoid or who had previously suffered from the disease. The source of infection was a woman in the early stages of typhoid fever who had prepared the mayonnaise dressing used on the chicken salad.

A Comparative Study of State Regulations for the Control of Influenza. FEEZER—(*Public Health Reports*, 1920 xxxv) collected data on the subject discussed by means of a questionnaire and presents the following summary of conclusions: (1) Great divergence of practice exists on practically all features of influenza control as represented by the regulations and other measures which are in force throughout the country. (2) It is noticeable that 97.5 per cent. of the forty states considered require some system of reporting. The reports are made to the local health officer in 74.4 per cent. of these states; to

the state health officer in 12.8 per cent.; and to both in 12.8 per cent. The method is the same in 92.3 per cent., namely, by mail. (3) There is a great division in practice in quarantine methods, also in regard to placarding. (4) A noticeable fact with regard to the closing of public places in time of epidemic is a tendency to shift the responsibility to the local health authorities. A number of comments which were received in addition to the straight answers to the questions indicated a growing inclination to the view that closing is useless. (5) On the matter of public funerals the practice is fairly equally divided. (6) Relative to the use of serum, it is very clear that public health authorities, almost without exception, are unwilling to undertake the responsibility of making any recommendations whatsoever.

Studies of Reconstructed Milk.—STEVENSON, PECK and RHYNUS (*Public Health Reports*, 1920, xxxv, 2011) present the following summaries of the study: Under manufacturing and handling: (1) Reconstructed milk and cream made from skimmed milk powder, unsalted butter, and water have been produced in large quantities at Nitro, W. Va., and sold to the public. (2) The cost of manufacturing these products in the Southern States is less than the cost of local normal milk. As the distance between the points of efficient production and consumption is lessened, this difference in cost becomes less. In the dairy sections at the present time fluid milk can be sold more cheaply than reconstructed milk. (3) Reconstructed milk products serve as excellent emergency supplies, and as soon as the process of manufacturing milk powder is perfected they will no doubt compete in the open market with normal milk products. Under the analytical study: (1) Studies of the bacterial content of this plant's output of reconstructed milk and cream show that it was satisfactory from a health standpoint. (2) It has been demonstrated that satisfactory ice cream can be manufactured on a commercial scale, with a bacterial content comparable to that of well-pasteurized milk and cream. (3) Using the revolving coil type of ice-cream batch mixer for mixing the ingredients entering into reconstructed milk, a product of homogeneous fat content cannot be made, and the final product from an entire batch should be mixed before bottling.

Sunlight in the Sterilization of Tuberculous Sputum.—TÉCON (*Paris méd.*, 1920, x, 33) placed sterilized sand, gravel and dust on a terrace with southern exposure at Leysin, Switzerland, and dropped upon it sputa from consumptive patients, previously examined for tubercle bacilli. Meteorologic data were recorded at short intervals throughout the experimental period. Sputa thus exposed to the mountain sun in the summer for periods of from two to over fifty-two hours—the experiment in the latter case extending over nine days—all gave positive results when subsequently inoculated into guinea-pigs; in some instances, however, the onset of tuberculous disease was considerably delayed. All the experiments but one were conducted in cloudless weather. In another series of tests sputum was exposed to the sun on beaten snow. In these tests the sputum was regularly rendered sterile in less than twenty-nine hours. The marked discrepancy between the temperature by day and night in this series is thought to have been

a factor in the sterilization, but there are other possible factors, such as reflection, ultraviolet rays, etc. In one experiment sputa from the same patient and with approximately equal bacterial content were exposed simultaneously on snow and on the above mentioned reproduction of an ordinary footway. After twenty-three hours of isolation on the latter medium the sputum gave positive results in guinea-pigs, while after like exposure on beaten snow inoculations were negative. This shows that the difference between temperatures by day and night cannot be the sole factor in the more rapid sterilization upon exposure over snow. The general conclusion from the experiments is that the sterilizing value of sunlight on tuberculous sputum discharged upon public highways is practically negligible in the summer time; it is more marked on sputum discharged on mountain roads during the snowy season.

The Effect of Shaking Alkalinized Aqueous Solutions of Arsphenamin and Aqueous Solutions of Neoarsphenamin in the Presence of Air.—Roth (*Public Health Reports*, 1920, xxxv, 2205) showed experimentally that shaking solutions of arsphenamin and neoarsphenamin in the presence of air led to marked increase of toxicity of the drugs. Preparations which are difficultly soluble should, for this reason, not be shaken as a dangerous increase in toxicity may result. Warning is given against preparing solutions in a mortar or large beaker as is sometimes practised.

Bacteriologic Characteristics of Tubercle Bacilli from Different Kinds of Human Tuberculosis.—Griffith (*Jour. Pathol. and Bacteriol.*, 1920, xxiii, 129) states that the main objects of his investigations were (1) to determine by the examination of unselected cases the relative proportions of the human and bovine types of tubercle bacilli in different kinds of human tuberculosis, and (2) to ascertain the frequency of occurrence and the distribution in the human body of variant strains of tubercle bacilli. Of 1068 persons examined, 803 showed human bacillus infection, 194 bovine bacillus infection, and 5 a mixed infection. Of various regions involved the examination showed that bovine infections occurred as follows: Bones and joints, 19.7 per cent.; genito-urinary organs, 17.65 per cent.; cervical glands, 46.3 per cent.; meninges, 20 per cent.; scrofuloderma, 34.65 per cent.; lupus, 48.9 per cent. As to the age periods, bovine infection occurred as follows: During the first five years of life, 37.55 per cent.; from five to ten years, 29.45 per cent.; from ten to sixteen years, 14.66 per cent.; after sixteen, 6.25 per cent.

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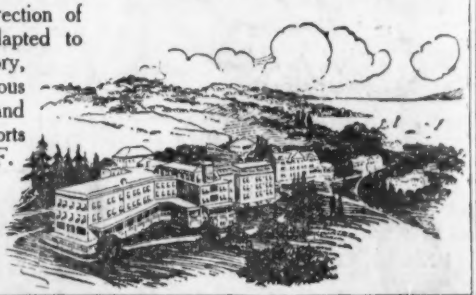

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